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Review

Naltrexone: A review of existing sustained drug delivery systems and emerging nano-based systems

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ABSTRACT

Narcotic antagonists such as naltrexone (NTX) have shown some efficiency in the treatment of both opiate addiction and alcohol dependence. A few review articles have focused on clinical findings and pharmacogenetics of NTX, advantages and limitations of sustained release systems as well as pharmacological studies of NTX depot formulations for the treatment of alcohol and opioid dependency. To date, three NTX implant systems have been developed and tested in humans. In this review, we summarize the latest clinical data on commercially available injectable and implantable NTX-sustained release systems and discuss their safety and tolerability aspects. Emphasis is also laid on recent developments in the area of nanodrug delivery such as NTX-loaded micelles and nanogels as well as related research avenues. Due to their ability to increase the therapeutic index and to improve the selectivity of drugs (targeted delivery), nanodrug delivery systems are considered as promising sustainable drug carriers for NTX in addressing opiate and alcohol dependence.

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1. Introduction

Treatment options for heroin addiction has long been dependent on three main alternatives namely detoxification, opioid agonist (*i.e.* methadone) and partial agonists (*i.e.* buprenorphine) maintenance treatment, and oral NTX. Detoxification followed by long-term residential treatment was found to cause some reduction in drug use but suffered from problems such as lack of retention in treatment and risk of overdose upon discharge [1]. Opioid maintenance treatment (OMT) involves the administration of opioid agonist medications such as methadone, buprenorphine and medically dispensed heroin under supervision [2]. OMT has been effective in decreasing mortality rates, morbidity and drug-related criminal activity. However, dropout rates remain quite high during the initial months of treatment.

As regards alcohol abuse, detoxification, non-pharmacological (psychosocial) treatment methods and pharmacotherapy have not been very effective. Disulfiram (Antabuse®), Naltrexone (Revia®), and calcium acetylhomotaurinate (Acamprosate®) are the three major oral pharmacotherapies used in the treatment of alcoholism. Disulfiram is a deterrent medication and makes its ingestion unpleasant. Acamprosate®, a glutamate antagonist has been found promising in the treatment of alcoholics [3,4] but present limitations. For some patients, combination therapy with NTX or disulfiram have proved to be effective [5].

The development of long-acting depot formulations of NTX has led to improved results such as increased bioavailability and efficacy of treatment and is considered as a solution to the problem of non-compliance and extensive first pass metabolism associated with oral NTX. This has been summarized in two excellent review papers [6,7]. In their review, Lobmaier et al. [6] emphasized on NTX depot formulations for opioid and alcohol dependence, discussing the mode of administration, the pharmacokinetic properties, safety and tolerability of the systems. The authors concluded on the need for further research on NTX to effectively block clinically relevant doses of heroin. Krupitsky et al. [7] summarized the effectiveness and safety of long-acting sustained release injectable and implantable formulations of NTX for heroin dependence. The authors concluded on improved tolerability and effectiveness of long-acting sustained-release NTX systems compared to oral NTX. They also mention that studies comparing the injectable formulation with oral NTX are required. In both reviews, the delivery systems are limited to NTX-loaded polymer-based microspheres.

This article reviews existing naltrexone delivery systems and their limitations and presents benefits of emerging nano-based delivery systems. In the first part of the review, we present the mechanism of action of NTX and its interest as a substitute for methadone followed by an in-depth analysis of commercially available NTX formulations with more recent references based on clinical trials through 2011 to 2013. We have summarized safety and tolerability aspects of extended-release formulations to ease access to information. We also stress on new nano-based NTX developments such as block copolymer micelles and cross-linked nanogels that attract a lot of interest and opens up new perspectives for research.

2. Current treatment against opiates and alcohol dependency

Opiates generally refer to any of the narcotic opioid alkaloids found as natural products in the opium poppy plant, *Papaversomniferum* [8]. Few examples of opiates include heroin and codeine. Opiate drugs act both in the central and peripheral nervous systems and opiate-dependent patients show impairment in brain functioning [9,10]. Agonists and partial agonists such as methadone and buprenorphine respectively, and antagonists such as NTX have been used in the management of opioid dependence.

2.1. Agonist therapy: methadone and associated problems

Methadone was first developed in Germany in 1937. However, its use as a substitute for heroin in the management of heroin dependence was not until 1964 [11]. Methadone has cross tolerance with other opioid compounds such as heroin, morphine and codeine and can therefore be used as a chemical replacement for the illicit opioid. The treatment of opioid addicts with methadone involves an initial methadone maintenance program (MMT). MMT is the most widely used opioid substitution program for the management of heroin dependence and its clinical efficacy has been repeatedly shown by several studies [12]. Being long acting, methadone should be administered only once daily as opposed to heroin which requires twice or thrice daily dose administration. Its oral route of administration substantially reduces the potential risks of spreading Hepatitis C or HIV. However, methadone therapy has few limitations.

Methadone therapy is associated with a number of problems. Due to its full μ opiate receptor agonist action, there is no limit to the level of respiratory depression or sedation that methadone can induce. As a result, methadone overdose can be lethal, with risk being particularly high during the induction period [13]. The combination of methadone with other opioid drugs, benzodiazepines or alcohol increases the risks of sudden cardiac death [14] and death by anoxic brain injury with pulmonary edema secondary to respiratory depression [15]. Methadone may increase the likelihood of QT interval prolongation [16] and may be associated with torsades de pointes [17] that can be fatal.

As methadone has a long half-life, coming off methadone is associated with a longer period of opioid withdrawal symptoms than when coming off heroin. This results in a significant degree of discomfort in patients who attempt to stop methadone. Methadone is a corrective but not a curative treatment for opioid addiction. Newer treatments with opioid antagonists like long acting NTX formulations need to be explored further as the initial results look promising.

2.2. Partial agonist therapy: buprenorphine and associated problems

Buprenorphine is a partial μ agonist and κ opiate receptor antagonist. It is also used in the treatment of opioid dependence and has several potential benefits over MMT. It is less sedating than methadone due to the fact that it is a partial μ receptor agonist. Also, it is associated with lower overdose risk since it rarely causes respiratory depression when used alone [18]. One way of reducing the abuse liability of buprenorphine [19] without affecting its bioavailability has been *via* the addition of naloxone hydrochloride to buprenorphine in a ratio of 1:4 (Suboxone, Reckitt Benckiser) [20]. Suboxone® was approved in April 2006 by the Therapeutics Goods Administration (TGA), and is now largely replacing buprenorphine hydrochloride (Subutex®) as the principal formulation for ambulatory clinical treatment of opioid dependence. Buprenorphine is available in different forms as summarized in Table 1.

New dosage forms of buprenorphine include transdermal patches [22], orodispersible or mucoadhesive buccal films [23]. The transdermal buprenorphine patch, Transtec®, first launched in 2001 uses a matrix technology whereby buprenorphine is homogeneously incorporated in a solid polymer matrix patch [22]. Transdermal buprenorphine patches are available in three different dosages with total loading doses of 20 mg, 30 mg, and 40 mg which release the drug at a controlled rate of 35 μg/h, 52.5 μg/h and 70 μg/h respectively [22]. BUNAVAIL™ is the first and only buccal formulation of buprenorphine and naloxone [24]. A New Drug Application (NDA) was submitted to the Food and Drug Administration (FDA) in 2013 and is currently under review.

A consensus on the relative superiority of buprenorphine over MMT remains elusive. Many studies reveal no significant differences between the treatments [25]. Others report significantly higher rates of retention in treatment, and abstinence from, or reduction in illicit opiate consumption among buprenorphine patients than among MMT patients [26]. A few studies described more favorable outcomes for MMT than

Table 1
Different forms of buprenorphine.

Trade name	Dosage form	References
Subutex® (buprenorphine)	Sublingual tablet (2 mg and 8 mg)	[21]
Suboxone® (buprenorphine/naloxone)	Sublingual film (4 mg buprenorphine/1 mg naloxone and 12 mg buprenorphine/2.5 mg naloxone)	
Zubsolv® (buprenorphine/naloxone)	Sublingual tablet (2 mg buprenorphine/0.5 mg naloxone and 8 mg buprenorphine/2 mg naloxone)	
Transtec®	Transdermal	[22]
Butrans®	Transdermal (delivering 5, 10 or 20 g/h)	[23]
Norspan ®	Transdermal (delivering 5, 10 or 20 g/h)	

for buprenorphine in terms of retention, abstinence for at least three weeks, opioid-free urine [27], and cost-effectiveness [28]. Nevertheless, overall pharmacokinetic features suggest that buprenorphine is safer than MMT, with respect to its reduced risk of respiratory depression, withdrawal symptoms, and accidental opioid overdose deaths [29] and reduced potential for abuse [30].

2.3. Antagonist therapy: naltrexone and its mechanism of action

Narcotic antagonists such as NTX, have been found useful in the treatment of both opiate addiction and alcohol dependency [31,32]. NTX has a chemical structure similar to opiates and can occupy the body's opiate receptors in preference to opiates. The ability of NTX to effectively antagonize heroin use is unequivocal [33,34]. Studies have reported serum NTX levels of 2.8 ng/ml as being effective in blocking 500 mg of snorted pure pharmaceutical diamorphine [35], serum naltrexone levels >2 ng/ml [34–38] as being effective in blocking the effects of 25 mg intravenously administered heroin, and others have reported plasma levels of less than 1 ng/ml as being capable of antagonizing the effects of 15 mg morphine [39].

NTX is an opioid receptor antagonist that blocks the reinforcing effects of opioids and reduces alcohol consumption and craving. Historically, N-allylnorcodeine was the first opioid antagonist-like molecule developed in 1915. It acted by blocking the respiratory-depressant effects of morphine and heroin. In the 1940s, nalorphine was the first reported opioid antagonist but was found to cause dysphoria, discouraging its use in the treatment of opioid intoxication and overdose. Naloxone was then developed in 1960 as a less toxic antagonist. It did not cause any dysphoria but suffered from short duration of action and poor oral bioavailability. To circumvent these disadvantages, NTX was developed in 1963 by Endo Laboratories, which was later acquired by DuPont. It is generally synthesized from thebaine (an opiate alkaloid) [40] and was found to have better oral bioavailability, a longer duration of action and twice as potent as naloxone. Naltrexone hydrochloride is freely soluble in water, slightly soluble in ethanol (approximately 96%), and practically insoluble in methylene chloride [41]. It is a BCS Class IV drug *i.e.* it has low solubility and low permeability.

Table 2 gives a summary of the pharmacokinetic data of NTX. NTX is FDA-approved for the treatment of alcoholism or opioid addiction in the form of commercially available oral tablets *e.g.* Trexan®, Revia®, Depade® or the long-acting, high-dose depot form Vivitrol® for intramuscular injection.

Table 2
Pharmacokinetic data of NTX [37,42].

	Naltrexone
Chemical formula	$C_{20}H_{23}NO_4$
Oral bioavailability	Up to 40%
Metabolism	Hepatic
Peak concentration	1–2 h
Half-life	Up to 14 h (oral)
Duration of action	Up to 24+ h
Elimination	Hepatic metabolism and renal excretion
Peak plasma level	1 to 2 ng/ml

Studies have revealed that the mesolimbic dopamine system is the prime target of addictive drugs. This system originates in the ventral tegmental area (VTA) of the brain (Scheme 1). Most projection neurons of the VTA are dopamine-producing neurons. GABA interneurons suppress dopamine cell firing resulting in reduced dopamine release. Opioids block the inhibitory control exerted by these neurons over the VTA dopamine cell bodies resulting in increased VTA dopamine activity, thus enhancing brain-reward (reinforcement circuit in the human brain) and inducing drug-taking behavior and possibly drug-craving. Each addictive drug has a specific molecular target which engages a distinct cellular mechanism. The main molecular receptors of opioids are μ-OR G_{io} protein-coupled receptors.

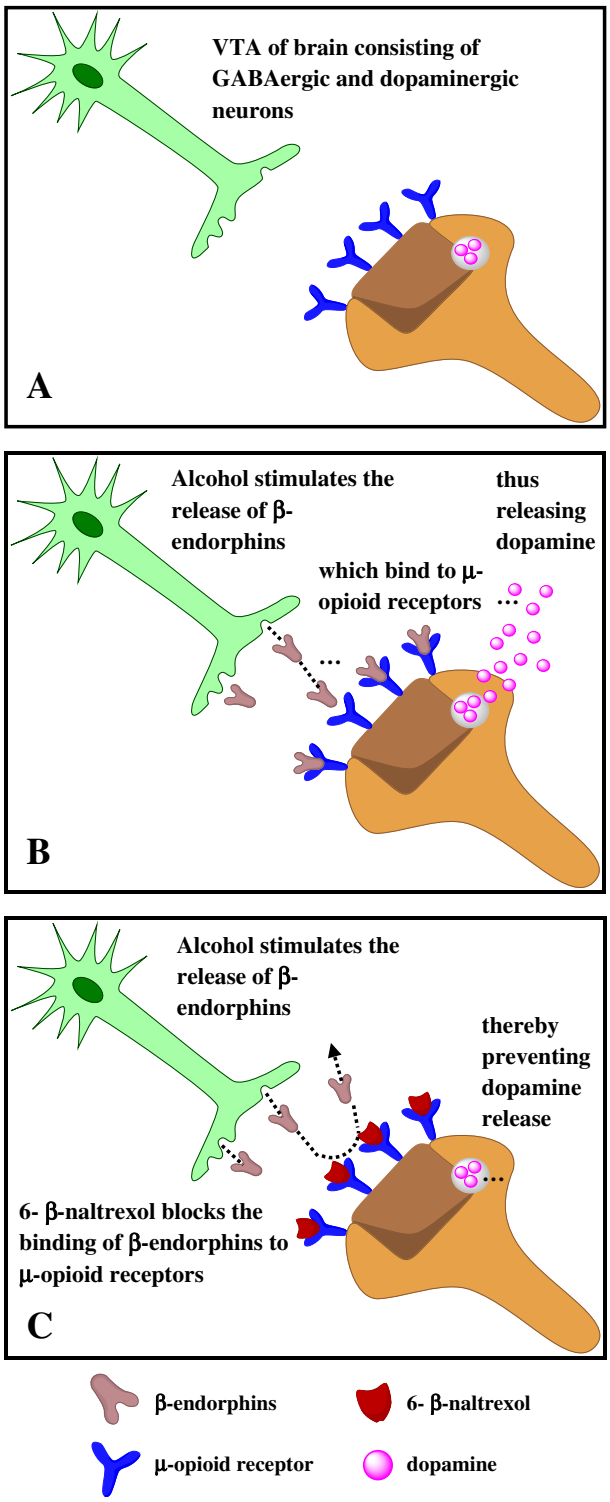
NTX acts by blocking the μ-opiate receptors, thus reducing craving. The precise mechanism for craving reduction has not been determined yet, but it is likely that NTX causes antagonism of opioid pathways to the nucleus accumbens, thereby reducing the total amount of dopamine released (Scheme 1). In addition, opioid antagonists like NTX influences other biological systems such as G-receptor second messenger systems [43], immune system [44] and the HPA axis [45]. NTX is metabolized in the liver into a variety of metabolites, with 6-β-naltrexol being the metabolite useful in treating drug abuse (Scheme 2). 6-β-naltrexol is believed to act as a competitive antagonist at opioid receptors. Cytochrome P450 enzymes, which are involved in the metabolism of methadone or buprenorphine do not play a role in NTX metabolism. NTX is largely metabolized by the aldo-ketoreductase family of enzymes (AKR1C1, 1C2 and 1C4) [46] with AKR1C4 being the most efficient [47]. It is believed that a polymorphism of the AKR1C4 enzyme is responsible for inter-individual variability in 6-β-naltrexol levels and could be used to explain the efficacy of and compliance with NTX treatment [46].

Due to its higher potency compared to naloxone and cyclazocine, NTX is considered as the most promising narcotic antagonist used for the treatment of narcotic addiction [48,49]. A minimum plasma level of NTX of 1 ng/ml is required for blocking clinically relevant doses (*e.g.* 25 mg) of intravenously administered heroin [50]. Evaluation of a program where cognitive behavioral therapy (CBT) and/or NTX were used over 12 weeks showed that addition of NTX significantly improved the abstinence rate (36.1% CBT against 62.6% CBT + NTX) [51].

However, oral NTX (Revia® tablets) has been associated with high early dropout rates. It was shown that 37% of patients discontinue daily oral NTX by 12 weeks [52] and more than 80% discontinue use by 6 months [53]. As demonstrated by several studies, compliance is critical for the efficacy of NTX [54]. Moreover, orally administered NTX has poor bioavailability due to high hepatic metabolism (98%) and a wide fluctuation in drug plasma concentration occurs with orally administered NTX [55]. Indeed, a review of the effectiveness of oral naltrexone maintenance for the treatment of opioid dependence concluded that there was insufficient evidence to justify the use of NTX in maintenance treatment of opioid addicts [56].

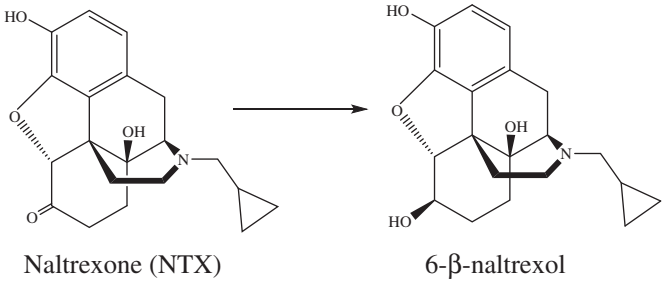
3. Limitations of oral NTX

As mentioned earlier, NTX is available commercially as tablets for oral administration. However, they have several pharmacotherapeutic limitations. First of all, more than 98% of the drug is metabolized in the liver and very small amount reaches the brain. Due



Scheme 1. Schematic representation of interplay between GABAergic and dopaminergic neurons in (A) absence of drug of abuse and its antagonist, (B) presence of drug of abuse only and (C) presence of both drug of abuse and its antagonist.

to extensive first pass metabolism, the concentration of naltrexone and the active metabolite, 6-β-naltrexol peaks within the first hour after oral dosing, followed by a steady decline each day during treatment [57]. This explains the need for the development of a system whereby NTX bypasses the liver *i.e.* an injectable long-acting drug delivery system. Such a system will enable the maintenance of a constant and predictable drug plasma concentration. According to a study conducted



Scheme 2. Metabolism of NTX to 6-β-naltrexol.

by Verebey et al. [55] among alcoholics, drug plasma levels fluctuates much with orally administered NTX. In fact, a 100 mg naltrexone dose provided 96%, 86.5% and 46.6% blockade at 24 h, 48 h and 72 h respectively. Moreover, the use of oral NTX places the onus on the patients as to whether to take the medications or not and very often, they do not comply with the required frequency. Studies have also shown that a comparatively low proportion of patients choose to start NTX treatment [58]. Among those who do, many drop out early; one quarter after a few days [33] and as many as half in the first few weeks of treatment [59]. This is a major problem given that several studies have demonstrated that missing even a few doses of NTX could lead to full relapse into opioid use and discontinuation of the treatment, despite intensive clinical interventions [54,60].

4. Drug delivery: basic principles

Drug delivery systems (DDS) may be differentiated according to the way the drug is administered or released. They may be administered through oral or parenteral (intravenous, intramuscular, subcutaneous, intradermal or intraperitoneal) routes [61].

DDS can broadly be classified as immediate release and modified release dosage forms. Modified-release systems can be further divided into delayed-, extended- and targeted-release systems. Furthermore, extended-release systems can be divided into sustained- and controlled release systems [61] (Fig. 1).

Sustained release systems maintain the rate of drug release over a sustained period of time [61]. Sustained release systems may be either in the form of reservoir or matrix systems. Reservoir systems often follow a zero-order kinetics (linear release as a function of time) while matrix systems often follow a linear release as a function of the square root of time. Sustained release systems offer several advantages such as reduced fluctuations in drug concentrations, and reduced total dose. Also, the patient does not require taking the drug frequently and therefore resolves the issue of non-compliance.

Controlled-release systems are different from sustained-release ones [61]. They are designed to maintain specific plasma concentrations, independent of the biological environment of the application site [61,62]. Another major difference is that sustained-release forms are often restricted to oral dosage forms. On the other hand, controlled-release systems are used in a variety of administration routes, including transdermal, oral and vaginal administration [61].

Release from oral NTX tablets may be termed as a burst release, resulting in fluctuating plasma concentrations during the day (Fig. 2). NTX concentration peaks within the first hour of oral dosing followed by a fairly rapid decline in plasma levels to below the minimum therapeutic levels (2 ng/ml) within 8 h of dosing [63]. The use of a sustained release NTX formulation will result in slow NTX release, avoiding the peaks and troughs associated with daily drug administration, while maintaining continuous therapeutic plasma levels for an extended time frame. This "smoothing out" of drug levels in the blood may decrease the possibility of occurrence of adverse events associated with peaks, and improve efficacy by avoiding drug concentration troughs.

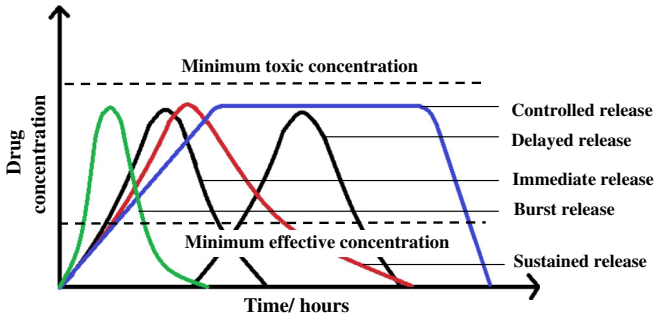


Fig. 1. Drug release kinetics.

Drug release may be modeled using different models as shown in Table 3 [64]. The R^2 values are used to check which model best fits the release system.

Polymer based drug delivery systems may be categorized as diffusion-controlled, solvent-activated (swelling or osmotically controlled), chemically controlled or externally-triggered (*e.g.* pH, temperature) [65].

Immediate-release, modified-release, extended-release and delayed-release have been defined by the FDA. However, no definitions have been provided for targeted or controlled release [61].

Barzegar-Jalali et al. reported on a general model applicable to multi-mechanistic release from nanoparticles (Eq. (6)) [66]. Parameters obtained from this model may be used to compare different delivery systems of a given drug as well as correlating with bioavailability data. Indeed, the release half life, $t_{50\%}$ can be used to compare release rates of different systems. The values of the different parameters obtained for NTX-loaded hydrolyzable crosslinked nanoparticles (using Eq. (6)) are given in Table 4. The $t_{50\%}$ value obtained for the more hydrophobic PEO–MMA copolymer (1:4) suggests a more sustained release compared to the PEO–MMA copolymer (1:1).

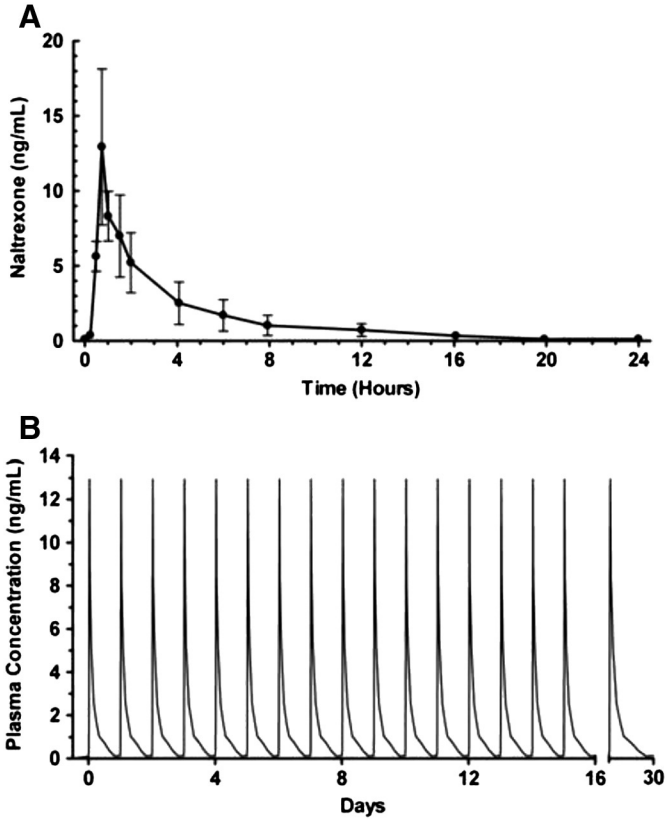


Fig. 2. (A) Typical profile of plasma NTX levels over 24 h following a 50 mg oral dose in humans. (B) Simulation of the daily fluctuations in plasma levels of NTX over the course of a month, assuming the patient adheres to the daily dosing of oral NTX. Reprinted with permission from [63].

Table 3
Kinetic models used for analysis of drug release data.

Model Name	Model	Overall mean percent error
Zero order	$M_t = M_0 + k_0 t$	18.28
First order	$\log C_t = \log C_0 - Kt/2.303$	16.41
Higuchi	$M_t = K_H t^{1/2}$	10.65
Hixson–Crowwell	$M_0^{1/3} - M_t^{1/3} = \kappa t$	26.63
Power law	$\ln F = \ln K_p + p \ln t$	7.66

M_t: amount of drug dissolved in time t.
M_0: initial amount of drug in the solution.
k_0: zero-order release constant.
C_t: concentration of drug dissolved in time t.
C_0: initial concentration of drug.
K: first order rate constant.
t: time.
K_H: Higuchi dissolution constant.
κ: constant incorporating the surface-volume relation.
F: fraction of drug released at time t.
p, K_p : parameters of the model.

$$\frac{1}{F} - 1 = \frac{m}{t^b} \tag{6}$$

The use of kinetic models helps to elucidate release mechanisms, which can in turn be useful to control drug release. The mathematical models discussed above can help optimize existing systems and ultimately design a polymer-based therapeutic system with the drug released at the required rate and concentration.

5. Sustained-release NTX formulations

An alternative NTX maintenance delivery against the problem of non-compliance involves injection or surgical insertion of a sustained release preparation of NTX, avoiding the gastro-intestinal route. This removes the need for daily oral NTX.

5.1. Sub-cutaneous formulations

The concept of sustained release preparations of NTX is not new. Beginning in the mid-1970s, a number of depot formulations of NTX were developed. While showing promising NTX release patterns, and being of 'likely biodegradable materials', most had unacceptable tissue compatibility. For example, Chiang et al. [67] conducted one of the early studies of sustained release NTX in normal, healthy volunteers implanted subcutaneously with naltrexone-copolymer (90% L-lactic acid and 10% glycolic acid) beads. Following an initial burst of release, this formulation yielded relatively constant plasma levels of NTX (0.3–0.5 ng/ml) for up to 1 month. Data indicated that this NTX preparation had unacceptable levels of biocompatibility, with two of the three human subjects implanted with the naltrexone-copolymer (90% L-lactic acid and 10% glycolic acid) beads having

Table 4
Summary of parameters obtained for NTX release using the reciprocal powered method [66].

Nanosystem	N[a]	R^2	E	m	b	$t_{50\%}$ (h)
PEO–MMA copolymer (1:1)	6	0.895	3.0	1.967	0.603	3.1
PEO–MMA copolymer (1:4)	17	0.650	10.5	3.559	0.431	19.0

N: number of data in each set.
E: percent error.
F: fraction of drug released in time t.
m, b: parameters of the model.

them removed at approximately 3 to 4 weeks due to marked inflammatory reactions or other local tissue irritation. Chiang concluded that this result "may preclude the clinical use of this particular preparation of beads" [67].

5.2. Injectable formulations

Newer formulations of sustained-release NTX have provided more promising results. Injectable formulations of NTX, such as those produced by Biotek, Inc. (Depotrex®; [68]), Drug Abuse Sciences (Naltrel®; [69]) and Alkermes, Inc. (Vivitrex®; [70]) appear to produce both clinically relevant plasma concentrations of NTX (1–2 ng/ml) for approximately 3–6 weeks, with clinically acceptable incident level of tissue reactivity. For example, an injectable depot formulation of NTX (Depotrex®, 192 mg, 384 mg NTX base) antagonized the effects of intravenously-administered heroin (0–25 mg) for 3–5 weeks, depending on NTX dose. This study demonstrated that Depotrex® was safe, effective, and well tolerated in opioid abusers who were not seeking treatment for their drug use. A subsequent "proof-of-concept" clinical trial of Depotrex® in treatment-seeking heroin abusers showed a robust, dose-related increase in treatment retention, supporting the effectiveness of NTX in antagonizing the objective and subjective effects of heroin [71].

5.3. Novel implants and depot injections

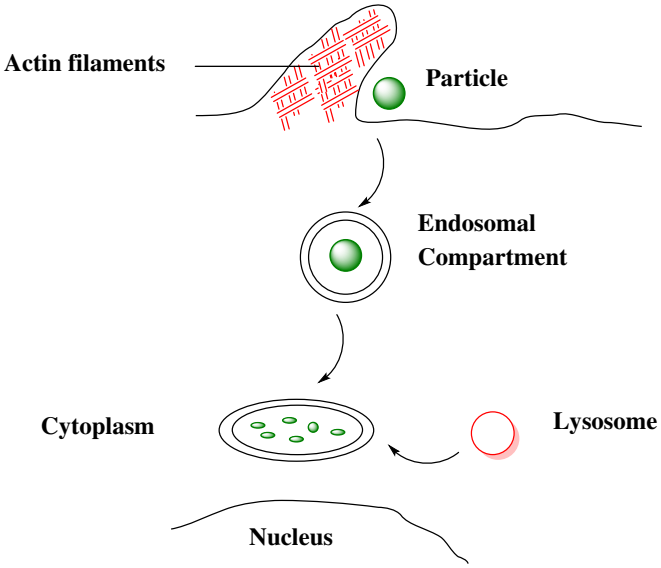
Recently, extended-release formulations that release NTX for 1–7 months have become available for clinical use. Such systems consist of compressed NTX or NTX/polymer/copolymer administered sub-cutaneously or intra-muscularly [72]. Most studies have indicated the effectiveness of these systems which have acceptable adverse event profiles [50]. A 30 day injectable NTX, Vivitrol® was approved by the FDA for treatment of alcohol dependence or opioid dependence in 2006 and 2010, respectively. It was shown that patients who received 400 mg treatment during 28 days had a blood NTX level of 1.23 ng/ml [73]. A larger 6-month trial of Vivitrol®: (205 received 380 mg injections, 210 received 190 mg injections, 209 received placebo injections, plus psychosocial intervention) also reported a reduction of 25% ($p = 0.03$) in heavy drinking days in the 380 mg NTX, and 17% ($p = 0.07$) in the 190 mg dose compared to placebo recipients. However 36% of patients failed to complete the 6-month course of monthly injections, with the majority of these lost to follow-up after 60 days [74]. However, a dose dependent effect was observed for the injectable formulation of NTX [75,76]. More recently, four well designed randomized clinical trials have provided clinical data that a number of sustained release NTX formulations using depot injection [71,77], or implant [78–80] have good clinical efficacy. An intra-muscular injectable NTX depot formulation with a mean plasma NTX level above 1 ng/ml for 21 days [81] falling to 0.58 ng/ml by 6 weeks [82] was tested over 3 months in alcohol dependent persons [83]. Although the NTX group ($N = 158$) had longer time to first drinking day and higher abstinence rates than the placebo group ($N = 157$), approximately 25% of the NTX group failed to return after their second monthly treatment. A sub-cutaneous implant based on NTX/PDLA microspheres was also developed by Go Medical Industries, an Australian Company. The implant formulation incorporates NTX-loaded poly [trans-3,6-dimethyl-1,4-dioxane-2,5-dione] (DL) lactide microspheres compressed into tablets and surrounded by a poly-(DL)-lactide coating to form the implant. NTX release from the implant was found to be 1–2 ng/ml, for 3 and 5 months with the 10-pellet and 20-pellet implants respectively, and reached 7 months with the 30-pellet ones [84]. Surgical procedures required to insert the implant may cause wound infections, local site reactions and scars [80]. Most of the NTX implants lack approval for regular clinical use. In summary, although these studies show that depot NTX formulations overcome the daily medication noncompliance issue associated with oral NTX, and produce good treatment outcomes, the requirement that patients return for re-treatment every 30 days [74,85] is associated with high attrition rates post 60 days (25–36%) and limits clinical efficacy.

6. Sustained-release systems for NTX delivery

Currently, there are two main types of sustained-release technologies for NTX release: injectable intramuscular suspension and surgical implantable pellets. Such delivery systems offer various advantages compared to conventional dosage forms including improved efficacy, reduced toxicity, improved patient compliance and convenience. Similarly as for free NTX, NTX-based sustained release systems need to be able to cross the blood–brain barrier (BBB) for them to be effective. As reported by Misra et al. [86] long circulating properties of drug carriers and appropriate surface characteristics to allow interactions with endothelial cells are crucial when designing a brain delivery system. The intracellular fate of sustained-release formulations is vital since the therapeutic effect of most drugs occurs in specific locations within the cell. In general, the drug must cross one or various biological membranes before diffusing through the plasma membrane to finally gain access to the appropriate organelle where the biological target is located [87]. On the other hand, depending on their physico-chemical characteristics, larger particles such as nanoparticles or polymeric micelles are internalized either *via* endocytosis [87], whereby the particles are completely encapsulated within a lipid bilayer isolating them from the cytosol.

To avoid phagocytosis, the particles should be small with a hydrophilic surface. Ligands may be attached to the nanoparticle's surface to regulate uptake through non-phagocytotic routes. Release of the drug into the enzymatic environment of the lysosomes or directly in the cell cytoplasm will, indeed have an important impact on the pharmacological activity. According to Plapied et al. [88], internalization of microparticles (>1 μm) occurs *via* macropinocytosis as summarized in Scheme 3. Macropinocytosis occurs *via* formation of actin-driven membrane protrusions. However, unlike in the case of phagocytosis, the protrusions do not zipper up along the ligand-coated particle but instead, they collapse and fuse with the plasma membrane. Knowledge about cellular uptake mechanisms is vital as this can lead to better stability of nano- and microparticles (reduced phagocytosis) as well as preserved biological activity of labile drugs [89].

The section below provides a summary of data from literature on currently available sustained release NTX formulations.



Scheme 3. Internalization of microparticles *via* macropinocytosis.

7. Sustained-release NTX implants

Development of sustained-release formulations started three decades ago [39]. In 1984, Wise et al. developed a naltrexone (70%)/poly(D,L-lactide-*co*-glycolide) copolymer (30%) implant system, the first biodegradable drug delivery system approved by the FDA for clinical testing. However it was limited by a "burst release" observed in human trials. The advantage of sustained-release NTX is that doses are required less frequently, potentially reducing rates of non-compliance, between-dosage withdrawal and relapse [90].

A number of sustained-release NTX implants have been developed to overcome the limitations of oral NTX. These are generally inserted in the sub-cutaneous tissue of the lower abdominal wall under local anesthesia. There are three different forms of NTX implant manufactured by Australian (Go Medical Industries), Russian (Fidelity Capital) [91], American (Wedgewood Pharmacy) [92] companies respectively. The Russian Federation is the only one who has approved the regular use of NTX implants outside of research settings [6].

According to Krupitsky et al. [7], Prodetoxone® is the only one registered and its use is restricted to Russia only. Prodetoxone® and Wedgewood® implants are based on a magnesium stearate matrix while the O'Neil® implant uses a biodegradable polymer matrix system. A report on the Wedgewood® implant suggests blocking levels at 5 ng/ml about 3 weeks after surgical insertion [35].

Pharmacokinetic studies with Prodetoxone® containing 1 g NTX, also showed that a therapeutically significant NTX blood level could be achieved with levels above 20 ng/ml despite considerable inter-individual variation [93]. Wedgewood® implant containing 1 g of NTX and compounded with magnesium stearate (Wedgewood Pharmacy, Sewell, NJ) has been reported to release NTX at levels above 1 ng/ml during 30–60 days [94].

O'Neil® implant consists of sets of 10, 20 or 30 pellets containing a poly(lactic acid)-based polymer and NTX at doses of 1.1, 2.2 or 3.3 g (O'Neil Implant®, Go Medical Industries, Perth, Australia). NTX release is found to be 1–2 ng/ml, for 3 and 5 months, respectively with the 10-pellet and 20-pellet implants and reaches 7 months with the 30-pellet ones [84]. In a study conducted by Hulse et al., it was concluded that the O'Neil® implant had a longer pharmacokinetic action than the Wedgewood® implant [95]. Indeed, data showed that blood NTX levels are maintained above 2 ng/ml for a significantly longer time period for the O'Neil® implant (114 days) compared to the Wedgewood® implant (30 days).

Both *in-vitro* and *in-vivo* drug release from NTX implants have been studied by several research groups [84,93,94]. Table 5 summarizes important features of the three implants.

Few RCTs on implantable NTX systems carried out will be here reviewed. Three RCTs used a 6-month version of the O'Neil® implant. An open-label study was carried out in a Norwegian treatment setting to evaluate the safety and effectiveness of NTX implant in reducing opioid use after in-patient treatment [79]. The 6-month study showed significant decreases in heroin use. This result was further supported by a placebo-controlled, double-dummy design with oral NTX in Western Australia [78]. A Norwegian open-label study compared the effects of NTX implants and methadone treatment in heroin-dependent inmates [96]. Dropout issues and reductions in opioid use among the patients were noted. Two randomized studies using Prodetoxone® have been conducted in Russia. A 10-week study consisting of 100 amphetamine and heroine dependent patients was carried out by Tiihonen et al. [97]. Significant reductions in heroin use were noted with retention rates of 52% and 28% for patients who received NTX and placebo implant respectively. A larger study that followed (n = 306 opioid dependent patients) over 6 months in a three-group, double-dummy design found that a significantly larger proportion of urine samples were opioid-negative in the NTX implant group compared to both oral NTX and placebo [98].

While the pharmacotherapeutic characteristics of NTX implants are well established [99], their biodegradation profiles have been less well defined. In a study by Hulse et al. [100], biodegradation of the NTX implant was found to follow several distinct phases. 'New' implants demonstrated clear boundaries between the implant tablets. As the biodegradation proceeded, a blurring of the external surface of the tablets and loss of the internal ring pattern were noted. It was hypothesized that both external and internal biodegradation occurred simultaneously. In advanced degradation the separation between the individual tablets disappeared, resulting in a single mass-like structure with its margins becoming increasingly indistinct.

Histological tissue changes over time around the site of the O'Neil® implant has also been investigated by Hulse et al. [101]. An early phase (up to 12 months post-implant) of inflammation, foreign body reaction, and fibrosis was noted. The study results demonstrate the implant's biocompatibility by the lack of inflammation, foreign body reaction, and fibrosis detected by 25+ months. Moderate fat necrosis was observed as a common feature of biopsies carried out during the first 6 months following implant. It was suggested that the surgical technique rather than the implant itself caused the fat necrosis. The latter subsided to mild levels over the next 18 months and was notably absent by 25+ months. Collectively, these data provide evidence of the *in vivo* absorption of the O'Neil® implant over time and its biodegradability in humans.

8. Sustained-release NTX injections

Injectable NTX preparations are administered every four weeks intramuscularly in the gluteal region. Different formulations, containing NTX-loaded microspheres of polylactide (Naltrel®, DrugAbuse Sciences, Inc, Paris, France) or polylactide-*co*-glycolide (PLGA) (Vivitrol®, Alkermes, Inc, Cambridge, MA; Depotrex®, Biotek, Inc, Woburn, MA) have been clinically tested [57,79]. Table 6 summarizes the properties of sustained-release formulations.

Vivitrol® is a PLGA based polymer formulation and contains 380 mg NTX. After intramuscular injection, NTX is released from the polymer microspheres *via* diffusion and polymer degradation. Release of NTX into blood plasma takes place in different stages. The initial phase occurs in the first 24 h and releases surface drug from the injection site. Afterwards, the injection site undergoes hydration within 48 h of injection and a sustained-release phase occurs over 30 days post-injection whereby drug is released *via* polymer microsphere erosion [102]. Plasma levels are not significantly dependent on weight, creatinine clearance, age, gender, or hepatic function [103].

Another significant issue related to extended-release injectable NTX is the avoidance of first-pass metabolism to 6-β-naltrexol. Plasma NTX levels after dosage with long-acting injectable NTX formulations consistently stays above 2 ng/ml longer, a cited therapeutic level for opioid relapse prevention [35,79].

Table 5
Summary of important features of implants.

Trade name	Mass of NTX in implant (g)	Therapeutic level of NTX in blood (ng/ml)
Wedgewood Implant®	1	1
Prodetoxone® — (Fidelity Capital)	1	20
O'Neil Implant®, Go Medical Industries	1.1, 2.2 and 3.3 for 10, 20 and 30 pellets respectively	1–2

Table 6
Summary of properties of sustained release formulations.

Trade name	Polymer	Dosage
Naltrel®	PDLA	300 mg
Vivitrol®	PLGA	380 mg

A research only formulation based on poly(L-lactide) injected subcutaneously [50] has shown some improvements towards heroin blockade [104,105].

Studies using an injectable depot formulation of NTX to treat alcohol dependence report reduced alcohol consumption and higher abstinence rates among patients during the treatment period; however a significant number of patients fail to complete the full course of treatment injections [73,74,82,83]. For example, an early placebo controlled pilot evaluation of 25 alcohol dependent patients treated monthly for 4 months with a 30-day (400 mg) intramuscular injectable NTX formulation (Vivitrol®: mean blood NTX level of 1.23 ng/ml over 28 days) reported trends for reduced alcohol consumption and liver enzymes (GGT) in the NTX treated group but also that 32% of the NTX group failed to complete the 4 monthly study injections [73]. A six month trial of Vivitrol® (380 mg and 210 mg) injection showed a 25% reduction in heavy drinking [74]. This effect occurred within two days of the injection and persisted throughout the 24-week study [75].

9. Safety and tolerability of extended-release formulations

Again despite addressing issues of daily oral NTX non-compliance, these sustained-release formulations still rely on patients returning monthly for subsequent treatments over 4 to 6 months, with failure to return for subsequent treatment still remaining a potential problem [71]. Nausea, vomiting and muscle twitches have been experienced by patients using both oral NTX and sustained-release formulations [106,107]. However, the intensity of adverse effects is lower in the case of extended-release formulations compared to oral NTX since such systems release NTX gradually in the bloodstream at concentrations varying between 1 and 5 ng/ml compared to NTX blood levels 10–30 ng/ml following tablet intake [108]. Yoburn et al. [108] suggested that NTX increases the sensitivity of opioid receptors, thereby making the patients more vulnerable to heroin overdose than usual. However, findings from toxicological examinations comparing patients with or without prior NTX exposure were not in line with this hypothesis [109]. Patients treated with the intramuscular injection often experience site pain and a few of them experience more serious site reactions such as induration and infection. Hepatic health is a concern for patients infected with Hepatitis C. There is little proof to support the fact that extended-release NTX formulations in ordinarily administered doses are hepatotoxic. In fact, intramuscularly administered NTX injections were found to be well tolerated in alcohol dependent patients with hepatic impairment [57,110]. Finally, high cost of the implant limits its use. Furthermore, in 2008, there was a FDA alert notifying healthcare professionals of the risk of adverse injection site reactions in patients receiving NTX (Vivitrol®) [111].

Table 7 summarizes results obtained from various studies on NTX implants and injections. To date, there has been no random controlled trial to assess the effectiveness of NTX implants as a treatment for alcohol dependence.

10. Micelles and microspheres for sustained-release of NTX

Due to the above mentioned issues, considerable interests have been shown in recent years in the development of new drug delivery systems for NTX.

Since the pioneering work of Ringsdorf in 1984 on the use of amphiphilic block copolymer micelles for solubilizing anti-cancer drugs, various other systems such as spherical, worm-like, rod-like micelles and vesicles have been designed [115]. Polymeric micelles consist of two separated functional segments namely an inner core and an outer shell. The outer shell controls *in vivo* pharmacokinetic behavior, while the inner core is responsible for drug loading capacity, stability and drug release behavior [116]. They offer several advantages compared to conventional modes of drug delivery such as longevity in blood circulation due to their nano-size (10–200 nm in diameter). Furthermore, they can solubilize hydrophobic drugs suffering from poor water solubility. In addition, multiple drugs may be encapsulated in a single micelle. Micelles can also be modified through attachment of specific ligands for improved targeting efficiency [117]. It can be divided into two main categories namely hydrophobically assembled micelles and polyion-complex micelles [118]. Drug release from the micellar core occurs by two major pathways. These include micellar dissociation or water penetration followed by drug diffusion out of the inner micellar core [119]. The encapsulated drug is steadily released with a kinetic profile of zero-order. Such type of systems increases therapeutic efficiency and reduces side effects. Controlled drug release from micelles may be achieved by exploiting different surface or bulk erosion rates through a choice of biodegradable polymers and external triggers such as pH and temperature changes.

Table 7
Summary of major findings for NTX implants.

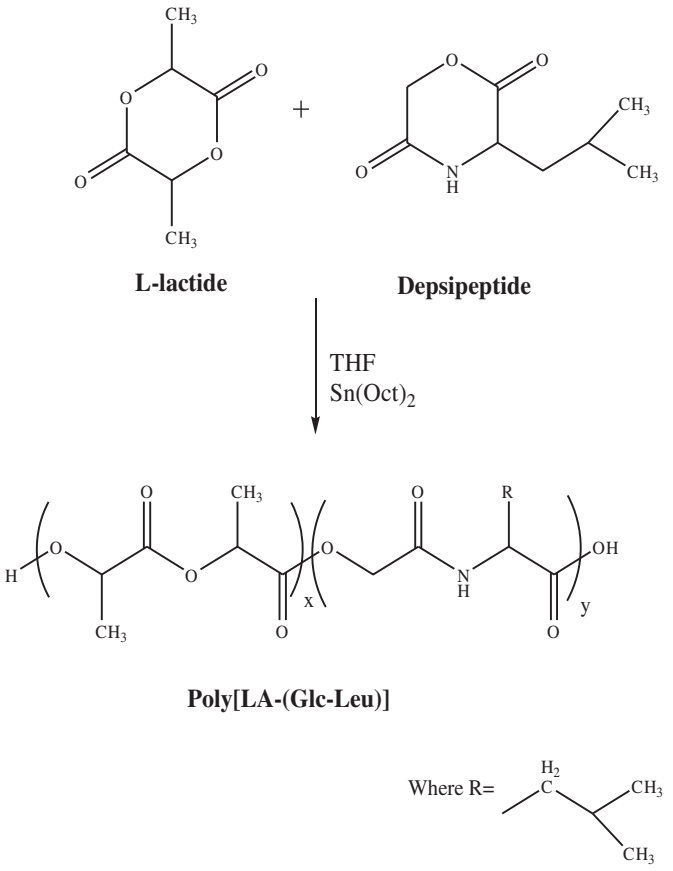
Target population and comparison group	Trade name of implant	Major findings — in terms of % relapse rates	References
Opiate-dependent patients	O'Neil®	Patients receiving NTX had on average 45 days less heroin use and 60 days less opioid use than controls in the 180-day period (both $P < 0.05$).	[79]
Opiate-dependent patients NTX implant v/s oral NTX		Opiate-positive urines at 6 months were lowest in the NTX implant group (63%) and higher in the oral NTX and placebo groups (87% and 86%, respectively).	[112]
Opiate-dependent patients NTX implant v/s oral NTX		More participants in the oral v/s the implant group had blood NTX levels below 2 ng/ml in months 1 ($P < 0.001$) and 2 ($P = 0.01$). More oral group participants returned to regular heroin use by 6 months ($P = 0.003$).	[78]
Opiate-dependent patients	Wedgewood®	The proportion of patients whose urine tested positive for NTX were 70%, 52% and 39% for Go Medical, Wedgewood NTX (1.1 g and 1 g) respectively	[113]
Amphetamine and heroin-dependent patients NTX implant v/s placebo implant	Prodetoxone®	52% patients remaining in treatment and 38% of patients having urine samples free of both drugs at 10 weeks compared to 28% remaining and 16% drug free for the placebo implant.	[97]
NTX implant (NI) v/s oral NTX (ON) or placebo implant (PI)		52.9% remained in treatment without relapse compared with 15.7% the PI + ON group and 10.8% in the PI + OP group ($P < 0.001$).	[98]
Alcohol-dependent patients	Vivitrol®	A reduction of 25% ($P = 0.03$) and 17% ($P = 0.07$) in heavy drinking days in the 380 mg and 190 mg dose respectively compared to placebo recipients.	[74]
Opiate dependent patients Vivitrol® v/s placebo group		Total abstinence was reported in 36% (Vivitrol®) v/s 23% in the placebo group.	[114]

Akala et al. [120] reported on the design of NTX-loaded PLGA microspheres capable of sustained drug release from 30 to 150 days. Size of microspheres ranges between 62 and 86 μm depending on the copolymer composition. They showed that molecular weight had no effect on drug release for copolymers of the same composition. The effect of copolymer composition becomes pronounced at high ratio of lactic acid (LA) to glycolic acid (GA), which may be due to alteration in the crystallinity, hydrophobicity, and biodegradability of the polyesters. Particle size decreased and loading efficiency increased with increasing hydrophilicity of the microspheres. *In vitro* degradation studies showed that the molecular weight value dropped dramatically between 50 and 100 days. The degradation process was significantly enhanced with increasing amount of glycolide unit in the copolymers. They also found that drug loaded microspheres degraded faster than an empty one possibly due to the plasticizing effect of the drug. Overall, release rates could be tailored by varying initial molecular weight of copolymers and ratio of LA:GA.

Core-shell smart microparticles composed of poly(N-isopropylacrylamide)-*b*-poly(L-lactide) (PNIPAAm-*b*-PLA) were developed by Salehi et al. [121]. Amphiphilic block copolymers were prepared by radical polymerization of PNIPAAm using 2-mercapthoethanol as the chain transfer agent. The resulting hydroxyl terminated PNIPAAm was then used as a macroinitiator in the ring opening polymerization of L-lactide in the presence of stannous octanoate. NTX was loaded into the nanoparticles. TEM images showed that the size of NTX-loaded microspheres ranged from 20 to 50 μm and increased to about 100 μm at 45 °C. This diameter change as a function of temperature was correlated with thermosensitive phase transition of PNIPAAm. The authors hypothesize that at higher temperatures, the thermoresponsive micelles tend to aggregate by strengthened hydrophobic interaction since the micellar outer shell (PNIPAAm segment) turns to be more hydrophobic. Drug loading content increased from about 60% to 85% with increasing PLA contents. *In vitro* release showed a small initial burst effect possibly caused by untrapped NTX distributed in the outer surface of the micelles or at the interface between the micelle core and corona or maybe due to the collapse of the hydrophilic segment of the copolymer near its LCST. *In vitro* release studies showed that 5 and 18% NTX were released after 24 h from the 30/70 PNIPAAm-*b*-PLA and 70/30 PNIPAAm-*b*-PLA copolymers respectively. Drug release from the copolymer micelles was slow indicating a low diffusion coefficient of NTX in the micellar core. At the end of 35 days, 45% and 10% of the initial NTX was found to remain inside the 30/70 and 70/30 formulations, respectively. In summary, *in vitro* release times could be tuned by varying the PNIPAAm to PLA ratio.

Pagar et al. [122] used a single emulsion solvent evaporation technique to fabricate copolymer lactide-depsipeptide poly[LA-(Glc-Leu)] microspheres. The synthesis of poly[LA-(Glc-Leu)] copolymers is summarized in Scheme 4. Average size of the microspheres ranged from 10 to 90 μm. Sustained release of NTX from the microspheres was observed. Entrapment efficiency was found to be lower at low polymer and stabilizer (PVA) concentrations. Particle size decreased with an increase in homogenization speed possibly due to increased collisions between the emulsion droplets and rapid breakdown into smaller droplets. Moreover, drug entrapment was found to be lower in smaller diameter microspheres. *In vitro* release studies showed an initial burst release of 49.3% from poly[LA-(Glc-Leu)] microspheres compared to 62.5% in PLA microspheres. At the end of 30 days, about 80% of NTX was released. Histological examination of NTX-loaded poly [LA-(Glc-Leu)] microspheres injected intramuscularly into the thigh muscle of Wistar rats showed minimal inflammatory reaction, indicating that NTX-loaded microspheres were biocompatible.

To conclude, few research groups have investigated the use of copolymer-based systems (micelles, microspheres, nanogels). Preliminary results have been discussed above. However, only a few of them have carried out *in vivo* studies and to the best of our knowledge, there are no ongoing pre-clinical trials.



Scheme 4. Synthesis of poly[LA-(Glc-Leu)] copolymer.

11. Nanogels

Drug delivery systems based on polymeric micelles suffer from instability and show very fast drug release behavior [118]. Therefore, to develop systems with sustained drug release ability, block copolymer micelles need to be further stabilized. One of the preferred ways to reach this goal is to cross-link either the core or the shell of the micelles to form nanogels. Nanogels are defined as nanosized networks of chemically or physically cross-linked polymers that can swell in an appropriate solvent [123,124]. Nanogels having similar core–shell structures as micelles can incorporate both hydrophilic and hydrophobic drugs, with their small size being suitable for site-specified delivery by intravenous injection. In addition, due to their cross-linked structure, nanogels exhibit high stability which makes them more suitable for application as sustained drug delivery systems.

Yin et al. [125] investigated the use of hydrolysable cross-linked PEO monomethyacrylate-*g*-poly(methyl methacrylate) diblock copolymers as nanoparticulate carriers. TEM images showed a cross-linked core surrounded by a ring formed by the polyethylene glycol tail of polyethyleneglycol monomethylether monomethyacrylate (PEO-MA) (Fig. 3). The loading capacity increased with increasing PEO-MA content possibly because NTX was solubilized and consequently, had higher solubility in water. At higher PMMA ratio, NTX was mainly dissolved in PMMA with the formation of organic phase of the micelles. *In vitro* release of NTX investigated in PBS (pH 7.4) was found to be dependent on the monomer feed compositions. Drug release was biphasic with an initial rapid release due to the presence of the drug on the surface (*i.e.* embedded on the free PEO tails of hydrolyzable cross-linked PEO–MMA nanoparticles) and a second stage due to the hydrolysis of the cross-linked hydrophobic core to release the encapsulated drug. Drug release was found to depend on the ratio of hydrophilic to hydrophobic components. The

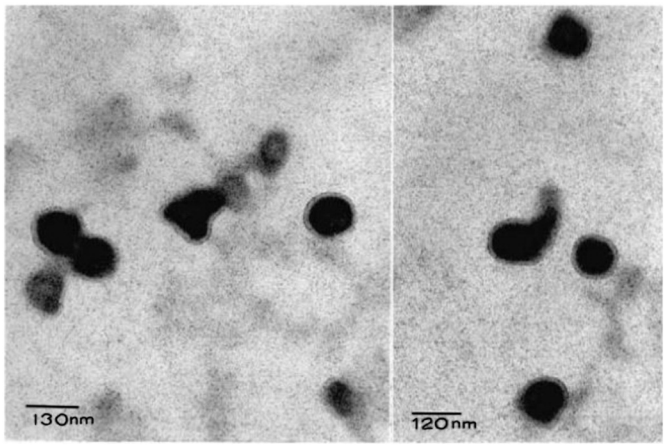


Fig. 3. TEM photomicrographs of NTX-loaded hydrolyzable crosslinked PEO–MMA nanoparticles.
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more hydrophobic cross-linked core of PEO–MMA hydrolyzed more slowly, resulting in smaller burst effect and a more sustained release of naltrexone. An initial burst release of 30–50% was observed for the nanoparticles compared to only 20% for the Australian implant. Moreover, the latter showed sustained release of NTX for a larger time period (over 2 months) compared to the nanoparticle based one (1 month).

In a study by Asadi et al. [126], nanogels were prepared by cross-linking of the terminal vinyl group of PLA–PEG–PLA diacrylate copolymers. SEM images showed that the nanogels formed spherical particles of around 200 nm (Fig. 4). Results showed that higher ratio of PLA/PEG block led to a higher amount of NTX loading, which could be largely due to hydrophobic nature of NTX which caused it to be encapsulated in the PLA core of the nanogels. Drug release studies demonstrated that a decrease of NTX release rate with increasing ethylene glycol dimethacrylate (EGDMA) cross-linker content (Fig. 5). This was attributed to more tightly packed core region of the nanogels.

Novel thermosensitive penta-block copolymer poly(N-isopropylacrylamide)-*b*-poly(ε-caprolactone)-*b*-poly ethylene glycol-*b*-poly(ε-caprolactone)-*b*-poly(N-isopropylacrylamide) (PNIPAAm-*b*-PCL-*b*-PEG-*b*-PCL-*b*-PNIPAAm) was synthesized by a combination of controlled ring-opening polymerization and atom transfer radical polymerization

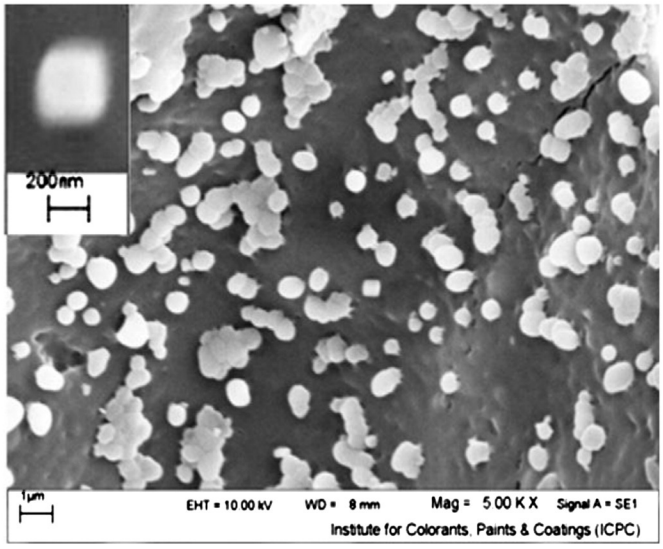

Fig. 4. SEM image of PLA_{48}–PEG_{45}–PLA_{48} nanogels with 50 wt.% EGDMA.
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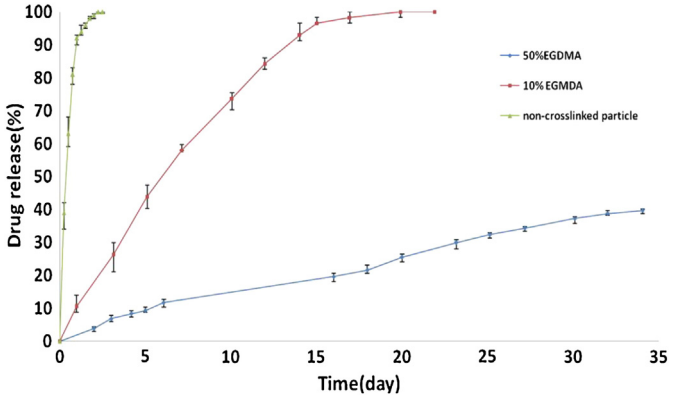

Fig. 5. NTX release profiles of PLA_{48}–PEG_{45}–PLA_{48} nanogels with different EGDMA concentration.
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(ATRP) by Abandansari et al. [127]. Reversible sol–gel transitions occurred between temperatures 22 °C and 37 °C (Fig. 6). The CMC value was 0.042 g/l as determined by fluorescence spectroscopy and the size of the micelles was approximately 20 nm. *In vitro* release studies from the hydrogels showed that slower release rate of NTX was obtained with higher initial drug loadings and higher hydrogel concentrations (Fig. 7). The cumulative release rate was found to decrease dramatically from 70.7% to 33.8% in 100 h when the initial loading of NTX was increased from 0.5 to 8 mg/ml.

12. Conclusions

The development of sustained-release NTX depot formulations aims at overcoming the problem associated with poor compliance of oral NTX. Several formulations were shown to release NTX above the suggested therapeutic plasma levels for time periods ranging between 1 and 7 months. The duration of NTX release at blocking levels from injectable and implant formulations is crucial, since NTX promotes abstinence from opioids and the risk of death from opioid overdose is increased upon relapse after prolonged abstinence. Most NTX implant formulations still lack approval for regular clinical use, thereby indicating the need for more data on safety and tolerability. New nano-based carrier systems such as nanomicelles and nanogels open up new perspectives for development but their efficacies remain difficult to assess as mostly limited to *in vitro* studies. Existing micellar systems such as PEG–Polyester, and PEG–Polypeptide or PVP–Polyester need to be tested for NTX encapsulation and delivery as well as new nano-micellar

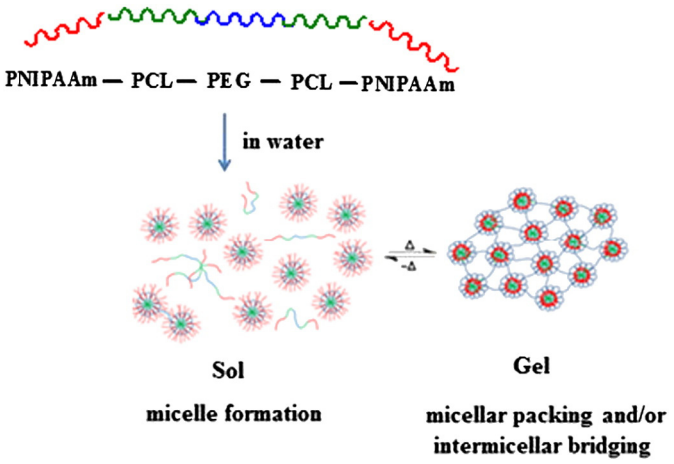

Fig. 6. Schematic representation of sol–gel transition of penta-block copolymer.
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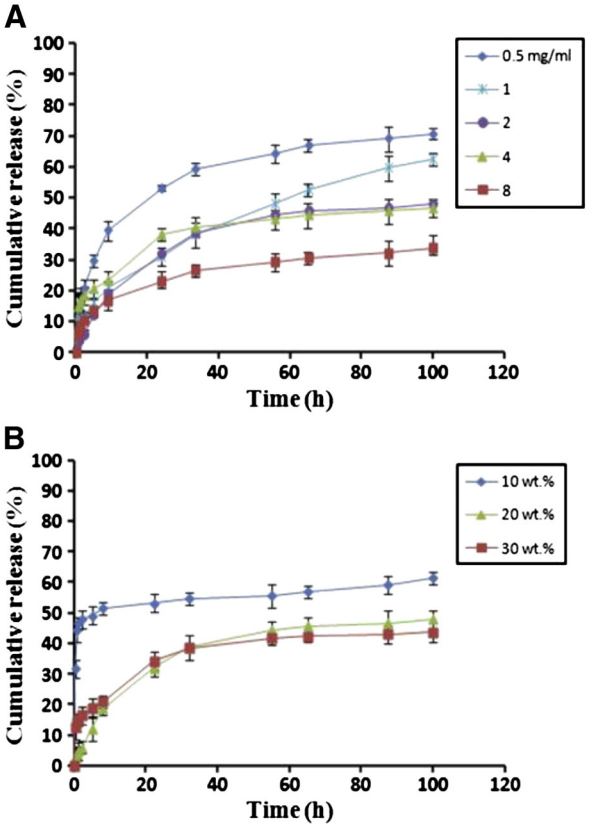

Fig. 7. *In vitro* release behavior of NTX from penta-block copolymer: (A) effect of initial NTX loading amount and (B) effect of hydrogel concentration.
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systems designed as carriers for NTX delivery. Moreover, the attachment of specific ligands such as dermophin [128], dynorphin, DADLE (Tyr-D-Ala-Gly-Phe-D-Leu), DSLET (Tyr-D-Ser-Gly-Phe-Leu-Thr), DTLET (Tyr-D-Thr-Gly-Phe-Leu-Thr) *etc.* [129] to target opiate receptors could lead to more effective delivery. Polymer–drug conjugates may also be considered for NTX delivery. Electrospun NTX-loaded polymeric nanofibers may be a promising option due to numerous advantages including the possibility of controlling drug release by careful selection of polymers and electrospinning processing parameters [130]. There is presently no work reported in these two areas. There is a need for PKPD data and bioavailability data of NTX-loaded nano-based systems. Finally, efforts have to be intensified to design sustained-release opiate systems that are cost-effective.

Acknowledgments

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