Journal of Advanced Biomedical and Pharmaceutical Sciences

Journal Homepage: http://jabps.journals.ekb.eg

Release Mechanisms for Profen-Loaded Nanofibers: Challenges and Opportunities

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Received: April 24, 2021; revised: August 26, 2021; accepted: August 31, 2021

Abstract

Nanofibrous meshes refer to the structures made of ultra-fine polymeric fibers. Because of nanometer measure size with an excessive strength/weight ratio, they are actual suitable as a nanosystem for delivering drug molecules. Drug molecules which mixed in nanofibers, can be released from the surrounding environment by means of various mechanisms in different manners (burst release, sustainable release and tunable release). Nanofibers can be used by way of release rate controlling strategies as proper delivery structures for drug molecules. The objective of this review is to highpoint the capacity of nanofibers as novel releasing substances for profens (Propionic acid derivative drugs including Carprofen; Naproxen; Fenoprofen; Flurbiprofen; Ibuprofen; Ketoprofen and Tiaprofenic acid). The *profens* are a class of nonselective, nonsteroidal anti-inflammatory drugs (NSAIDs). These drug molecules are derivatives of 2-phenylpropanoic acid. All contain a chiral center resulting in the formation of two enantiomers (R and S) of each profen. In this review, full information will be reported about the new progresses for release behaviors of profen molecules form the novel nanofibrous delivery systems. The drug releasing kinetics of profen molecules from nanofibers will be described briefly. The authors use more than 90 articles, books and thesis published in the case of nanofibrous profens delivery and releasing systems.

Key words

Nanofibers, Release characteristic, propionic acid derivative drugs, kinetic, sustainable release

1. Introduction

The releasing of the drug molecules from nanofibers is principally via two mechanisms which are displayed in Figure 1(1,2)

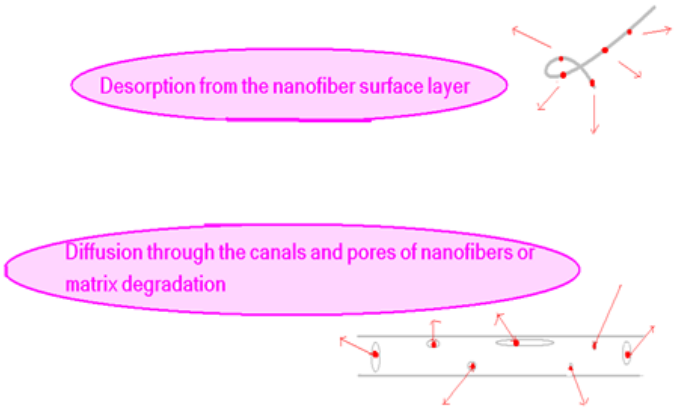

Figure 1: Mechanisms of controlling the drug release from nanofibers.

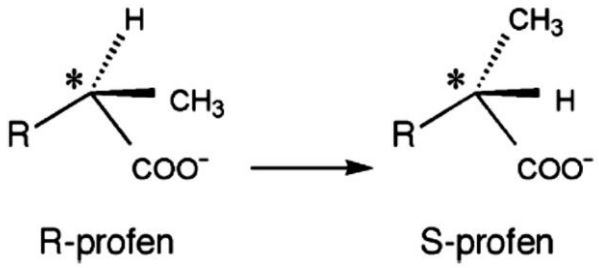

Figure 2: Propionic Acid Derivative Drugs (Profens) : General structures of R- and S-profens (The chiral centers are shown*).

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There are three chief styles for the releasing trends of drug molecules from nanofibers that will be displayed briefly:

I. *Sustained drug release*: means gradual releasing of drug molecules and active agents over a period of time, allowing for a sustained effect. Also means timed release. Slow release. Long-active, prolonged action(3).
II. *Burst drug release*: means sudden releasing of drug molecules permitting a rapid appearance of active molecules(4).
III. *Tunable drug release:* means a particular compositional or structural parameter is tuned to give a desired release profile(5).

For the delivery of antibiotic drugs, a great initial burst is reflected a benefit since it is essential for eliminating the interfering bacteria previously they implore to proliferate. (6, 7).

1.1. Drug related factors affecting drug releasing

Nanofibers can be used by way of release rate controlling strategies. Drug release from nanofibers could be because of desorption of drug from the surface layer, diffusion from pores and or matrix degradation (8, 9). Drug associated factors affecting its releasing form nanofibers are listed in next paragraphs(10).

a) *Drug loading content :* Generally, higher drug loading is connected with the faster release (11).
b) Molecular weight of drug: Low molecular weight drugs are recognized for their fast release rate (12).
c) *Physical state of drug:* The crystalline arrangement of the drug becomes deposited on nanofiber surface and offers burst release, whereas amorphous arrangement gets deposited deeper inside and get released in a sustained style (13, 14).
d) *Solubility of drug in the polymer matrix:* The higher the solubility of the drug molecules in polymer matrix, the slower the release (15).
e) *Drug—Polymer interactions* (*Chemical interactions like chemically bond drug or physical interactions like physically entrapped drug and physically adsorbed drug):* Almost physical interactions between the drug molecules and polymer matrix lead to a slower release. Furthermore, direct incorporation of drug molecules in nanofibers might possibly cause undesired burst releasing (16).

1.2. Nanofibers related factors affecting drug releasing

All procedures of drug release are possible to get affected by select of inactive (polymer or other material), porosity, morphology, and geometry of nanofibers(17, 18). Nanofibers related parameters affecting drug releasing form them are reported in next section(19).

A. *Randomization of nanofibers aligment:* Nanofiber alignment is a various factor recognized to mark drug release and generally randomized design is associated with quicker drug release owing to improved affinity of water uptake(20).
B. *Thickness of nanofibers:* The releasing of drug molecules are in reverse associated with the fiber diameters. Higher fiber diameter enhances the space that drug molecules placed in the central of fibers which must diffuse from side to side for reaching the edge of the fiber . This mechanism extends release times(21, 22). Usually smaller the diameter of nanofiber quicker the release rate is reflected from it based on the statement that reduced diameter fiber has advanced surface layer area and dissolution rate (23, 24).
C. Cristalinity of nanofibers : Crystalline domains of polymers are associated with slower release of drug molecules as compared to amorphous regions (25).
D. Molecular weight: The higher the molecular weight of the polymer, the slower the release of the drug molecules from the nanofibers (26).
E. *Porosity ratio of nanofibers:* The porosity of nanofibers appears to affect the releasing process. A greater porosity might increase the amount of fluid that absorbs to the nanofibers and therefore quicken the releasing. Nonetheless this result might have been repressed with other parameters like the amount of hydrophilicity of nanofibers. Also the size of pores and total volume of pores meaningfully influences the diffusion of the liquid which are absorbed on the nanofibers (27). Advanced conclusions recommended that drug release cannot be only run by means of diameter and simultaneously influence of porosity is to be considered. It is repeatedly revealed that thicker nanofibers with very high porosity releasing drug quicker as compared to thinner fibers with low porosity (28, 29).
F. *Specific surface area of nanofibers:* Upper specific surface area delivers a greater space for communication with the nearby fluid and resulting quicker releasing of drug molecules (30, 31).
G. *Fabrication method of the nanofibers (like co-electro spinning, side by side electro spinning, multi- jet electro spinning, co-axial electro spinning, emulsion electro spinning and surface immobilization):* Drug molecules can be encapsulated in the different layers of nanofibers in the different fabrication techniques, so this parameter plays an important character in manipulation of the location of drug molecules in the nanofibers, which can represent a promising controlled drug release system (32).

1.3. Analyzing of the drug releasing kinetics

Drug molecules mixed in nanofibers can be released from the surrounding environment by means of a blend of various mechanisms (33). Drug molecules on the nanofibre surfaces can be dissolved and spread out of the nanofibers sheath as it is entered with body fluids. Elimination of molecule drugs on fiber surface regularly matches to the burst phase of drug releasing. The amount of burst releasing might increase with the surface area on the nanofiber, so fibers with smaller fiber diameter or upper ratio of holes can have rapider burst release (34). The drug release kinetics can be modified by means of the selecting of polymer and controlling over the nanofiber diameter, porosity, geometry, and morphology with regulating the numerous processing variables during nanofibers production. For the assessment of the drug releasing kinetics and the determining of the mechanism in nanofibers, generally some equations are used like:

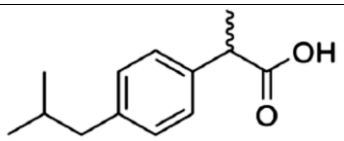
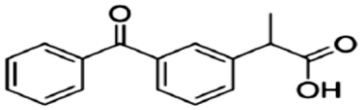
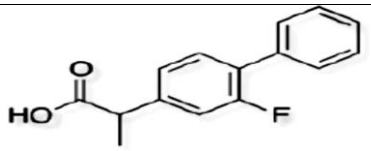
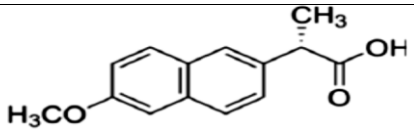
I. Peppas-korsmeyer equation (35),
II. Semi empirical releasing(srikar) model (36),
III. Crank model, siepmann model (37),
IV. Higuchi equation (38),
V. Siepmann and peppas model (39),
VI. Hopfenberg model (40, 41).

2. Propionic Acid Derivative Drugs (Profens)

The profens are a group of anti-inflammatory drugs. They reduce pain, body temperature in fever, signs of inflammation, and, in mice, slow the development of cancers. The profens are derivatives of 2-phenylpropanoic acid. All contain a chiral center resulting in the formation of two enantiomers (R and S) of each profen (Figure 2). The profens are accessible regularly as their racemates, viz., equal mixtures of the R and S stereoisomers (42)

There are a large number of profens available commercially including: Carprofen; Naproxen; Fenoprofen; Flurbiprofen; Ibuprofen; Ketoprofen; Tiaprofenic acid. In this review paper only some of them are investigated which are seen in Table 1(43).

Table 1. Chemical structures and physical/chemical properties of the studied profens(43).

Drug	Structure	IUPAC Name	Mol. Mass, g/mol	Tm, ˚C	pKa	logP
Ibuprofen		Iso-butylphenylpropionic acid	206	78	4.9	4.0
Ketoprofen		2-(3-benzoylphenyl)- propanoic acid	254	94	3.9	3.1
Flurbiprofen		2-(3-fluoro-4-phenylphenyl)-propanoic acid	244	111	4.4	4.2
Naproxen		(2S)-2- (6-methoxynaphthalen-2-yl)-propanoic acid	230	155	4.2	3.3
Chamazulene carboxylic acid (**1**)	—	A natural profen with anti-inflammatory activity and a degradation product of proazulenic sesquiterpene lactones, e.g., matricin.	—	—	—	—

3. Release characteristics of propionic acid derivative drugs (profens) from nanofibers

In a novel work, PLGA/ibuprofen nanofibers were electrospun into sandwich scaffolds. *Ibuprofen* molecules have a tendency for aggregating on the surface layer of nanofibres, so initial burst releasing is occurred throughout implantation. But the sandwiched scaffolds were expected to delay the diffusion of *ibuprofen* into liquids and reduce the initial burst release. These scaffolds displayed meaningfully a reduced initial burst of *ibuprofen* releasing in the first hour (44).

Hyaluronic acid/ibuprofen nanofibers were fabricated with electrospinning method. Sustained release of drug molecules from all nanofbers was detected throughout the initial day by 40–60% of ibuprofen molecule releasing after first day (45).

Gliadin/ibuprofen nanofibers were produced. In vitro experiments confirmed that the gliadin nanofibers with heterogeneous drug dispersal had less preliminary burst ibuprofen release and an extended time period releasing of 16 hours, signifying an improved sustained drug release profile than those nanofibers having a homogeneous drug dispersal that had plain initial burst release and a shorter release time period of 8 hour. The various ibuprofen dispersals have operated the different release performances of the loaded ibuprofen molecules, and therefore caused the dissimilar drug sustained release profiles (46).

PLA/ibuprofen nanofibers holding 10, 20, or 30 wt % drug were made. Two styles were seen while studying the release profiles. First, an increased temperature (37˚C) produced a superior release of ibuprofen from the nanofibers as compared to room temperature. Second, the 30 wt % ibuprofen overloaded nanofibers at 37˚C manufactured the highest ibuprofen release(~0.25 mg at 336 hours). At both room temperature and 37 ˚C, the results showed that a direct correlation occurred between ibuprofen concentration in the nanofibers and the quantity of ibuprofen released. PLGA/ibuprofen nanofibrous were designed. The ibuprofen releasing mechanism is combined of degradation and diffusion. Practically 30% of loaded ibuprofen released in around 8 hours without any initial burst release and then 50% of entire ibuprofen has been released throughout only 4 hours (47).

Polyvinylpyrrolidone/ibuprofen nanofibrous mats were constructed by means of an electrospinning method. The results specified that the ibuprofen molecules had respectable compatibility with the polymer and that ibuprofen was well dispersed in the nanofibers as an amorphous physical form (48).

Cellulose acetate/poly(vinyl pyrrolidone)/ibuprofen nanofibers were produced. These nanofibers showed a 3 phase releasing profile, an initial burst release, a succulents decelerating release and a constant release. Throughout the burst release phase, over 28 wt% of ibuprofen molecules were diffused from nanofibers that were owing to the distribution of ibuprofen molecules on the great surface of the nanofibers. At the succedent decelerating release phase, ibuprofen molecules in the internal of nanofibers diffused onto nanofibers surfaces. Through this procedure, ibuprofen molecules needed to overcome the Van der Waals' force (or dispersion forces) produced between ibuprofen molecules and polymer matrix that reduced ibuprofen diffuse rate. In the latest release phase, the small concentration difference of ibuprofen between receptor solution and nanofibers made the releasing of ibuprofen became more problematic (49).

PLLA/ibuprofen nanofibers which have small amount of Ag nanoparticles were fabricated. The *in vitro* drug releasing analysis indicated a sustained release of Ag ions and *ibuprofen* molecules from the nanofibers. Throughout the first 2 days, burst releasing of *ibuprofen* from the nanofibers was 49.5%, followed by a sustained releasing in the following 10 days. Briefly, *ibuprofen* releasing performance depends chiefly on polymer matrix degradation, drug diffusion and Ag releasing (50).

In another work, the Poly(N-isopropylacrylamide)/Poly(ε-caprolactone)/ibuprofen nanofibers were constructed with Tran et al. These nanofibers confirmed a variable and controlled releasing at both room and higher temperature. The rate at 22°C is 75% faster compared to that at 34°C. The results showed that 1 μmol of ibuprofen was rapidly released from these nanofibers in the first hour at 22°C, and then the rest drug was released at a considerable slower rate, 0.05 μmol hr^{-1}. Completely, 24% ibuprofen was released in four hours. In compare, ibuprofen was released at a more manageable style while the temperature was improved to 34°C. The average release rate was ~0.2 μmol hr^{-1} and ~ 0.4 μmol ibuprofen was released in the first one hour. Only 17% ibuprofen was released in 4 hours. This occurrence can be described with the great water solubility of Poly(N-isopropylacrylamide) when the temperature was below its LCST (32°C), leading to the rapid ibuprofen releasing from the polymeric matrix. Though, Poly(N-isopropylacrylamide) converts greatly hydrophobic after temperature was above its LCST. Therefore Poly(N-isopropylacrylamide) functions similar a drug depot to forbid the rapid release of hydrophobic ibuprofen molecules, resulting in the comparatively more manageable release style (51).

In a different investigation, the PLLA/PLGA/ibuprofen nanofibers were prepared. The outcomes of an *in vitro* ibuprofen releasing displayed a burst release throughout the first 2 days with high initial ibuprofen amount. This initial phase was followed by a sustained release stage from nanfibres during the subsequent 10 days (52).

PLA/ibuprofen nanofibers were created. Two tendencies were detected while examining the ibuprofen release profiles. In the first stage, an increased temperature (37˚C) produced a superior releasing of drug from the nanofibers as compared to room temperature. In the second stage, PLA/ibuprofen(30%) nanofibers at 37˚C produced the maximum drug releasing. In both room temperature and 37˚C, the statistics recommended that a direct association be presented between ibuprofen amount in the nanofibers and the quantity of drug molecules released (53).

Cellulose acetate/Poly(vinylpyrrolidone)/ibuprofen nanofibers were manufactured. These structures samples showed continued and steadily increasing release profiles (54).

Polycaprolactone/ibuprofen nanofibers were prepared with Potrcˇ et al (55).

The releasing of *ibuprofen* from the PCL nanofibers was fast, reaching about 96% of the overall *ibuprofen* release in the first 4 hours from the nanofibers. The drug release rates from the PCL nanofibers loaded with various quantities of *ibuprofen* were not meaningfully different, representing that the changes in the nanofiber diameters and the surface morphology did not affect the release of the *ibuprofen*(55). A drug release test *in vitro* showed that the release rate of ibuprofen and ketoprofen was slow in PCL nanofibers loaded with drug–layered double hydroxide nanoparticles. After 5 days, only 44–48% of ibuprofen was released, whereas the release of *ketoprofen* was 20–25%. All nanofibers could release the drug after 5 days (56).

Release behavior of profens from nanofibrous drug delivery systems will be described in Table 2.

Table 2: Drug release behaviors of profens from nanofibrous mats.

Material	Content load	Method	In vitro study		Reference
			Ibuprofen release		
			Burst release	Sustained release	
Cellulose acetate solved in acetone/DMAc	Naproxen 9.39%	Mixing	40% (in 2.5 hours)	100% (in 25 hours)	(57)
Polyvinylpyrrolidone solved in ethanol	ketoprofen	Mixing	100% (in 4 minutes)	---	(58)
Poly(vinyl alcohol) solved in deionized water	ketoprofen	Mixing	58.43% (in 2 hours)	83.82% (in 14 days)	(59)
Polyethylene oxide solved in methanol and water vapor; Silk and collagen solved in methanol and water vapor.	Polyethylene oxide containing Flurbiprofen **as sheath** with silk and collagen containing Vancomycin **as core**	Evaporation and coaxial process	33.1 μg/cm^2 Flurbiprofen (in 1 day) + 9.0 μg/cm^2 Vancomycin (in 1 days)	72.2 μg/cm^2 Flurbiprofen (in 9 days) + 33.4 μg/cm^2 Vancomycin (in 17 days)	(60)
Poly (N-vinyl caprolactam) solved in distilled water and ethanol	Ketoprofen 10%	Mixing	84% (in 4 minutes) at 20˚C 80% (in 4 minutes) at 42˚C	98% (in 2 hours) at 20˚C 100% (in 2 hours) at 42˚C	(61)
Poly(vinyl pyrrolidone) solved in EtOH and DMF; Poly(lactic-co-glycolic acid) solved in dichloromethane and DMF	Poly (lactic-co-glycolic acid) **as sheath** with Poly(vinyl pyrrolidone) containing Flurbiprofen 6% **as core**	Mixing and coaxial process	70% (in 24 hours)	85% (in 10 days)	(62)
	Ketoprofen	Mixing	50% (in 24 hours) in pH~2	73% (in 4 days) in pH~2	

Chitosan and polyaniline solved in acetic acid			70% (in 24 hours) in pH~6.7	90% (in 4 days) in pH~6.7	(63)
			72% (in 24 hours) in pH~7.4	97% (in 4 days) in pH~7.4	
Poly(vinylpyrrolidone) and zein solved in ethanol and water	Ketoprofen	Mixing and sequential process	32% (in 1 hour)	98% (in 16 hours)	(64)
Chitosan solved in acetic acid and water;	Naproxen 5%	Mixing	75% (in 10 minutes)	95% (in 4 hours)	(65)
Polyacrylic acid solved in sodium chloride and β-cyclodextrin;			25% (in 5 minutes)	30% (in 4 hours)	
Poly(caprolactone) solved in acetic acid and formic acid			50% (in 2 minutes)	95% (in 4 hours)	
Poly(vinyl alcohol) solved in water and phosphoric acid;	Naproxen 5%		25% (in 5 minutes)	38% (in 4 hours)	
	Naproxen 10%		40% (in 2 minutes)	48% (in 4 hours)	
	Naproxen 30%		50% (in 2 minutes)	70% (in 4 hours)	
Poly(lactic-co-glycolic acid) solved in N,N-dimethylformamide and tetrahydrofuran	Ibuprofen 5%	Mixing	23% (in 5 days)	80% (in 63 days)	(66)
Polyvinylpyrrolidone and ethyl cellulose solved in ethanol	Naproxen 20%	Mixing	30% (in 12 hours)	90% (in 3 days)	(67)
Pulp cellulose added to melted [BMIM]Cl	Ibuprofen 2%	Mixing and dry–wet process	48% (in 50 minutes) (irrespective of its content)	52% (in 8 hours) (irrespective of its content)	(68)
	Ibuprofen 3%				
	Ibuprofen 25%	Sol–gel	68% (in 10 minutes)	70% (in 7 hours)	(69)

Aluminum oxide added to distilled water and 2-butanol	Ibuprofen 50%		73% (in 10 minutes)	80% (in 7 hours)	
Poly(vinylpyrrolidone) solved in ethanol	Ibuprofen 10%	Pressurized Gyration	68% (in 10 minutes)	100% (in 10 hours)	(70)
Gelatin solved in acetic acid + Poly(lactic acid) solved in chloroform + Hydroxyapatite solved in water	Ibuprofen 33.2%	Mixing	30% (in 3 hours)	77±3.4 (in 3 days)	(71)
	Ibuprofen 38.9%		30% (in 3 hours)	87.2±3.4% (in 3 days)	
	Ibuprofen 41.2%		35% (in 3 hours)	81.3±4.6% (in 3 days)	
	Ibuprofen 45.3%		40% (in 3 hours)	92.1±2.8% (in 3 days)	
	Ibuprofen 58.2%		50% (in 3 hours)	95.8±2.1% (in 3 days)	
Poly(vinyl alcohol), Chitosan,ß-cyclodextrins	Ibuprofen	Supercritical carbon dioxide assisted phase inversion	60% (in 3 hours)	90% (in 24 hours)	(72)
Zein solved in methanoic acid	Ibuprofen	Blending	0.05 mg/ml^{-1} (in 90 min)	---	(73)
Poly(lactic acid) solved in dimethylformamide and chloroform	Ibuprofen 10%	Mixing	0.05 mg (in 1 day)	0.07 mg (in 12 days)	(53)
	Ibuprofen 20%		0.11 mg (in 1 day)	0.13 mg (in 12 days)	
	Ibuprofen 30%		0.21 mg (in 1 day)	0.25 mg (in 12 days)	
Cellulose Acetate solved in N,N-dimethylacetamide and acetone	Ibuprofen	Mixing	7.7% (in 4 hours)	---	(74)
Poly(caprolactone) solved in dichloromethyl and dimethyl formamide	Ibuprofen 10%	Mixing	98% (in 2 hours)	---	(75)

Poly(L-lactide) solved in dichloromethane and N,N-dimethylformamide	Ibuprofen 3.87 ± 0.31%	Mixing	15% (in 2 hours) in pH~5	30% (in 2 days) in pH~5	(76)
			10% (in 6 hours) in pH~7.4	20% (in 2 days) in pH~7.4	
Silk suture immersed in normal saline	Ibuprofen	Deposition on filaments and immersion	0.75/µg cm^{-1} (in 4 hours)	1.40/µg cm^{-1} (in 10 days)	(77)
Poly(l-lactic acid) solved in dichloromethane and N, N-dimethylformamide	Ibuprofen 3.91±0.22%	Mixing	40% (in 6 days)	80% (in 35 days)	(78)
Poly(lactide-coglycolide) solved in dichloromethane	Ibuprofen 10%	Mixing	1.6 µ moles (in 1 hour)	---	(79)
Cellulose Acetate solved in acetone/DMAc	Ibuprofen 7.1%	Mixing	20% (in 1 hour)	80% (in 1 day)	(80)
Poly(lactide-coglycolide) and poly(ethylene glycol)-g-chitosan solved in N,N-dimethylformamide	Ibuprofen 5%	Mixing	22% (in 1 day)	70% (in 16 days)	(81)
Poly(lactide-coglycolide) solved in N,N-dimethylformamide	Ibuprofen 5%	Mixing	45% (in 1 day)	100% (in 12 days)	
Poly(lactic-co-glycolic acid) solved in N,N-dimethylformamide and tetrahydrofuran	No load	Mixing	---	---	(66)
	Ibuprofen 5%		25% (in 3 days)	80% (in 45 days)	
			30% (in 1 day) in pH~5	45.09 ±4.02%	

Poly(vinyl pyrrolidone) and Lysine solved in milli-Q water	Ibuprofen 5%	Mixing	27.5% (in 1 day) in pH~8	(in 1 day) in pH~5 29.17 ±4.29% (in 1 day) in pH ~8	(82)
Polyvinylpyrrolidone solved in ethanol	No load Ibuprofen 7.5% Ibuprofen 15%	Mixing	---	---	(48)
Cellulose acetate and poly(vinyl pyrrolidone) solved in acetone and DMAc	Ibuprofen 20%	Mixing	30% (in 1 hour)	95% (in 1 day)	(49)
Gliadin solved in 1,1,1,3,3,3-hexafluoro-2-propanol and trifluoroacetic; Cellulose acetate solved in acetone and acetic acid	Cellulose acetate 0% Cellulose acetate 1% Cellulose acetate 3% Cellulose acetate 5% **as sheath** with gliadin containing Ibuprofen **as core**	Mixing and triaxial process; Mixing and coaxial process	34.2±4.5%(in1hour) 8.3±4.6% (in 1 hour) 5.4 ±4.1 (in 1 hour) 2.7± 3.1% (in 1 hour)	100% (in 2 days) (irrespective of its content)	(83)
Polyvinylpyrrolidone solved in distilled water	Ibuprofen 431.7 ± 39.7 µg/mL + 145.5 ± 5.6 µg/mL acetylsalicylic acid Ibuprofen 528.3 ± 24.7 µg/mL + 168.3 ±7.3 µg/mL acetylsalicylic acid	Mixing	---	---	(84)
Poly(caprolactone) solved in chloroform and acetone	Ibuprofen 9.1% Ibuprofen 13% Ibuprofen 23.1% Ibuprofen 28.6% Ibuprofen 33.3% Ibuprofen 37.5%	Mixing	72% (in 1 hour) 95% (in 1 hour) 87% (in 1 hour) 80% (in 1 hour) 83% (in 1 hour) 68% (in 1 hour)	100% (in 5 days) (irrespective of its content)	(55)

Poly(caprolactone) solved in dichloromethane and acetone	Ibuprofen 4.59%	Mixing	73% (in 1 hour)	75% (in 1 day)	(56)
	Ibuprofen 2.29%		40% (in 1 hour)	80% (in 1 day)	
Poly(l-lactic acid) solved in dichloromethane and *N*,*N*-dimethlformamide	No load	Mixing	---	---	(50)
	Ag 4%		23.5% Ag (in 2 days)	48% Ag (in 10 days)	
	Ag 4%+ Ibuprofen 4%		49.5% Ibuprofen (in 2 days) + 32.7% Ag (in 2 days)	88% Ibuprofen (in 10 days) + 72% Ag (in 10 days)	
	Ag 8%		35.9% Ag (in 2 days)	88% Ag (in 10 days)	
Poly(lactic-co-glycolic acid) and Poly(caprolactone) solved in dichloromethane and *N*,*N*-Dimethylformamide	Ibuprofen 5%	Mixing	75% (in 24 hours)	88% (in 13 days)	(44)
	Ibuprofen 10%		78% (in 24 hours)	90% (in 13 days)	
	Ibuprofen 15%		85% (in 24 hours)	96% (in 13 days)	
Gliadin solved in 1,1,1,3,3,3-hexafluoro-2-propanol	Gliadin **as sheath** containing Ibuprofen 6.25%	Mixing and traditional co-axial process	30% (in 2 hours)	95% (in 1 day)	(46)
	Ibuprofen 11.76% **as core**		35% (in 2 hours)		
Poly(caprolactone) solved in dichloromethane and acetone	Ibuprofen 2%	Mixing	40% (in 1 hour)	75% (in 1 day)	(56)
	Ibuprofen 5%		72% (in 1 hour)	90% (in 1 day)	
Poly(ethylene glycol) and Poly(caprolactone) solved	Poly(ethylene glycol) /Poly(caprolactone) containing Ag **as sheath** with hyaluronic acid containing Ibuprofen 0%	Mixing and core/shell process	50% Ibuprofen (in 8 hours) (irrespective of its content) + 80% hyaluronic acid (in 4 days) +	50% Ibuprofen (in 21 days) (irrespective of its content) +	(85)

in dichloromethane and *N*,*N*-Dimethylformamide	Ibuprofen 10% Ibuprofen 30% Ibuprofen 50% **as core**		78-81% Ag (in 4 days)	80% hyaluronic acid (in 17 days) + 19-22% Ag (in 17 days)	
Hyaluronic Acid solved in formic acid	Ibuprofen 0% Ibuprofen 20% Ibuprofen 30% Ibuprofen 40%	Mixing	--- 58% (in 24 hours) 52% (in 24 hours) 41% (in 24 hours)	--- 72% (in 20 days) 62% (in 20 days) 60% (in 20 days)	(45)
Poly (L-lactic acid) solved in dichloromethane	No load Ibuprofen	Mixing	--- 46% (in 12 hours)	--- 54% (in 20 days)	(86)
Poly(L-lactic acid)/Polyethylene glycol solved in dichloromethane and acetone	Ibuprofen 0% Ibuprofen 2% Ibuprofen 6% Ibuprofen 10%	Mixing	--- 38% (in 2 days) 47% (in 2 days) 62% (in 2 days)	--- 52% (in 18 days) 48% (in 18 days) 36% (in 18 days)	(87)

4. Physical aspects of profen loaded nanofibrous mats

Phisycal properties of profen loaded nanofibrous mats will be reported in Table 3.

Table 3: Physical characteristics of profen loaded nanofibrous mats.

Profen loaded nanofibrous mats	Ultimate stress(MPa)	Ultimate strain(%)	Young's modulus(MPa)	Reference
Poly(vinylpyrrolidone) + zein+ ketoprofen	12	14	---	(64)
Poly(lactic-co-glycolic acid) + Ibuprofen	---	140	---	(66)
Zein + Ibuprofen	0.6	99.7	---	(73)
Cellulose Acetate + Ibuprofen	---	34.36	---	(74)
Gelatin+Ibuprofen	0.8±0.1	---	1.5-2.0	(88)

Hyaluronic Acid+ 20% Ibuprofen	0.63 ± 0.53	61.46 ± 11.42	9.42 ± 0.83	
Hyaluronic Acid+ 30% Ibuprofen	0.94±0.89	81.22 ± 8.23	10.57 ± 0.84	(45)
Hyaluronic Acid+ 40% Ibuprofen	1.43±0.13	90.11 ± 8.75	14.16 ± 1.25	
Poly(lactic-co-glycolic acid) + Poly(caprolactone)+ 5% Ibuprofen	2.6	165	---	
Poly(lactic-co-glycolic acid) + Poly(caprolactone)+ 10% Ibuprofen	2.2	170	---	(44)
Poly(lactic-co-glycolic acid) + Poly(caprolactone)+ 15% Ibuprofen	1.7	180	---	
Poly(lactic-co-glycolic acid) + Poly(caprolactone)	2.2	170	---	
Poly(lactic-co-glycolic acid) + Ibuprofen	11.73±4.43	76.63±21.53	---	(47)
Poly(l-lactic acid)+Polyethylene glycol+ 2%Ibuprofen	3.42 ± 0.36	73.2 ± 3.6	60.4±3.9	
Poly(l-lactic acid)+Polyethylene glycol+ 6%Ibuprofen	3.13 ± 0.38	65.7 ± 3.2	65.8 ±5.1	
Poly(l-lactic acid)+Polyethylene glycol+10%Ibuprofen	2.89 ± 0.31	55.6 ± 4.2	69.3 ±4.6	
Poly(lactic-co-glycolic acid) +Ibuprofen	---	---	---	(44)

5. Structural characteristics of profen loaded nanofibrous meshes

Structural properties of profen loaded nanofibrous mats will be reported in **Table 4**.

Table 4: Structural characteristics of profen loaded nanofibrous mats.

Ibuprofen loaded nanostructure mats	Sample thickness (nm)	Pore size(μm)	Weight (mg/cm^2)	Porosity(%)	Water contact	Density (g/cm3)	Degree of swelling	**Reference**
Cellulose Acetate + Naproxen	409.3 ± 152.5	---	---	---	---	---	---	(57)
Poly(ethylene glycole) + Silk + Collagen + Flurbiprofen + Vancomycin	422 ± 74	---	---	---	---	---	---	(60)
Poly(lactic-co-glycolic acid) + Flurbiprofen	942	---	---	---	113	---	---	(62)
Poly(vinyl pyrrolidone) + Poly(lactic-co-glycolic acid) + Flurbiprofen	286	---	---	---	78	---	---	

Polyvinylpyrrolidone +Ethyl cellulose+20% Naproxen	409±89	---	---	---	---	---	---	(67)
Poly(vinylpyrrolidone) + 10% Ibuprofen	1500	---	---	---	---	---	---	
Poly(vinyl alcohol)+Chitosan+ß-cyclodextrins+Ibuprofen	---	0.7±0.3	---	37±1	---	---	---	(72)
Zein + Ibuprofen	605.6	---	---	---	---	---	---	(73)
Poly(lactic acid) + Ibuprofen 30%	585.38±131.51	---	0.69	---	---	---	---	(53)
Poly(lactic acid) + Ibuprofen 20%	478.31±167.61	---	0.67	---	87.9	---	---	
Poly(lactic acid) + Ibuprofen 10%	329.11±249.62	---	0.428	---	---	---	---	
Cellulose Acetate + Ibuprofen	533.5	---	---	---	---	---	---	(74)
Poly(caprolactone) + Ibuprofen 10%	374 ± 89	---	---	---	---	---	---	(75)
Silk + Ibuprofen	290 ±27	---	---	---	---	---	---	(77)
Poly(L-lactide) + Ibuprofen 3.87 ± 0.31%	1420	---	---	---	---	---	---	(76)
Poly(l-lactic acid) + Ibuprofen 3.91±0.22%	1350 ± 280	---	---	---	---	---	---	(78)
Hydroxypropyl-ß-cyclodextrin + Ibuprofen	180±95	---	---	---	---	---	---	(89)
Cellulose Acetate + Ibuprofen 7.1%	297 ± 14	---	---	---	---	---	600 %	(80)
Hydroxyapatite+ Ibuprofen	---	---	---	85	---	1.40		(88)
Poly(caprolactone)+Ibuprofen 9.1%	465± 88	---	---	---	---	---	---	
Poly(caprolactone)+Ibuprofen 13%	454± 83	---	---	---	---	---	---	(55)
Poly(caprolactone)+Ibuprofen 23.1%	593± 105	---	---	---	---	---	---	
Poly(caprolactone)+Ibuprofen 28.6%	568± 97	---	---	---	---	---	---	
Poly(caprolactone)+Ibuprofen 33.3%	582 ± 109	---		---	---	---	---	
Poly(caprolactone)+Ibuprofen 37.5%	686 ± 196	---		---	---	---	---	
Hyaluronic Acid+ 20% Ibuprofen	520 ± 16	---		---	---	---	---	(45)
Hyaluronic Acid+ 30% Ibuprofen	580 ± 17	---		---	---	---	---	
Hyaluronic Acid+ 40% Ibuprofen	630 ± 21	---		---	---	---	---	
Poly(l-lactic acid)	1020 ± 26	---		---	131.3° ± 3.1°	---	---	(50)

Poly(l-lactic acid) + Ag 4%	1140 ± 24	---	---	125.1 ° ± 4.1°	---	---	
Poly(l-lactic acid) + Ag 4%+ Ibuprofen 4%	1210 ± 37	---	---	126.8 ° ± 3.9°	---	---	
Poly(l-lactic acid) + Ag 8%	1180 ± 42	---	---	118.4 ° ± 2.7°	---	---	
Poly(lactic-co-glycolic acid) + Poly(caprolactone)+ 5% Ibuprofen	910±61	---	---	133.5	---	---	
Poly(lactic-co-glycolic acid) + Poly(caprolactone)+ 10% Ibuprofen	1150±59	---	---	134.2	---	---	(44)
Poly(lactic-co-glycolic acid) + Poly(caprolactone)+ 15% Ibuprofen	1150±59	---	---	134.2	---	---	
Poly(lactic-co-glycolic acid) + Poly(caprolactone)	860±40	---	---	135.9	---	---	
Cellulose acetate/Poly(vinylpyrrolidone)+Ibuprofen	385 ± 58	---	---	---	---	---	(54)
Poly (lactic acid) + 10% Ibuprofen	329.116 ± 249.62	---	---	---	---	---	(53)
Poly (lactic acid) + 20% Ibuprofen	478.316 ± 167.61	---	---	116.3	---	---	
Poly (lactic acid) + 30% Ibuprofen	585.386 ± 131.51	---	---	—	---	---	
Poly (ε-caprolactone)+ 10% Ibuprofen	1733	---	---	—	---	---	(51)
Poly (ε-caprolactone)+Poly(N-isopropylacrylamide)+Ibuprofen	551	---	---	—	---	---	
Poly(N-isopropylacrylamide)/ Ibuprofen	470	---	---	---	---	---	
Poly(l-lactic acid)+Polyethylene glycol+ 2% Ibuprofen	1.40 ± 0.52	---	67.5 ± 5.8	119.5 ± 3.1	---	---	
Poly(l-lactic acid)+Polyethylene glycol+ 6% Ibuprofen	1.32 ± 0.67	---	64.6 ± 8.1	121.9 ± 3.2	---	---	

Poly(l-lactic acid)+Polyethylene glycol+ 10% Ibuprofen	1.25 ± 0.59	---	61.6 ± 5.3	123.7 ± 2.6	---	---	
Poly(lactic-co-glycolic acid) + Ibuprofen	300±500	---	---	---	---	---	(47)

6. Kinetics of profen releasing from the nanofibrous webs

Table 5 represented the regression coefficients of mathematical models fitted to the releasing of profens from the nanofibrous mats.

Table 5: Suitable mathematical models fitted to the releasing of profen drugs from the nanofibrous webs.

Nanofibrous web	Mathematical model	Suitable equation	Closeness of fit (R^2)	Reference
Poly(ethylene glycole) + Silk + Collagen + Flurbiprofen + Vancomycin	Wei-bull	$C(t) = C_0\left[1 - exp\left(-\frac{(t - t_{lag})^1}{\tau}\right)\right]$	0.99	(60)
Poly(N-vinylcaprolactam) + Ketoprofen	Korshmeyer–Peppas	$M_t = 72.4415 \times t^{0.0760}$	0.9695	(61)
Poly(lactic-co-glycolic acid) + Poly(vinyl pyrrolidone) + Flurbiprofen	First order	$W = 52.50 \times e^{(-t/7.741)} + 68.13$	0.9820	(62)
	Zero order	W= 1.45t (in pH~2)	0.606	
		W= 2.27t (in pH~6.7)	0.550	
		W= 2.3t (in pH~7.4)	0.502	
	First order	log (100−W) = log 100−0.021t (in pH~2)	0.80	
		log (100−W) = log 100−0.044t (in pH~6.7)	0.954	
		log (100−W) = log 100−0.050t (in pH~7.4)	0.971	

Chitosan + Polyaniline + Ketoprofen	Higuchi	$W = 14.17t^{1/2}$(in pH~2)	0.967	(63)
		$W = 13.18t^{1/2}$(in pH~6.7)	0.993	
		$W = 8.984\,t^{1/2}$(in pH~7.4)	0.989	
	Hixson–Crowell	$(100 - W)^{1/3} = 100^{1/3} - 0.0245t$(in pH~2)	0.708	
		$(100 - W)^{1/3} = 100^{1/3} - 0.0433t$(in pH~6.7)	0.834	
		$(100 - W)^{1/3} = 100^{1/3} - 0.0496t$(in pH~7.4)	0.856	
	Korsmeyer–Peppas	$M_t/M_\infty = 0.109t^{0.567}$(in pH~2)	0.982	
		$M_t/M_\infty = 0.118t^{0.579}$(in pH~6.7)	0.992	
		$M_t/M_\infty = 0.107t^{0.675}$(in pH~7.4)	0.980	
Polyvinylpyrrolidone + Ethyl cellulose + 20% Naproxen		$Q_t = Q_0 + 1.03t$	0.9935	(67)
Cellulose + 3% Ibuprofen		$Qt = 8.3544t^{0.4231}$	0.9388	(68)
Cellulose + 2% Ibuprofen		$Qt = 18.527t^{0.2569}$	0.9906	
Poly (lactic acid)+ 15 mg Ibuprofen	Korsmeyer–Peppas	$M_t/Q_\infty = Kt^{0.40}$	---	(90)
Poly (lactic acid)+ 10 mg Ibuprofen	Korsmeyer–Peppas	$M_t/M_\infty = Kt^{0.30}$		
Poly (lactic acid)+ 5 mg Ibuprofen	Korsmeyer–Peppas	$M_t/M_\infty = Kt^{0.18}$		
Poly(vinyl alcohol)+Chitason+Ibuprofen	Korsmeyer–Peppas	$M_t/M_\infty = Kt^n$	0.96824	(91)

7. Conclusions and future perspectives

This review has widely presented releasing approaches of the propionic acid derivative drugs (profens) from nanofibrous drug delivery systems. Nanofibers can be used to deliver drugs, so as these ultra-fine structures are the novel materials that are capable as profen carriers in human body for numerous usages, for instance wound dressings. Moreover, they are appropriate for using in surgical sutures for pain reducing.

Conflict of interest

The authors declare that there is no conflict of interest regarding this review.

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