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Photo-irradiation paradigm: Mapping a remarkable facile technique used for advanced drug, gene and cell delivery

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ABSTRACT

Undoubtedly, the progression of photo-irradiation technique has provided a smart engineering tool for the state-of-the-art biomaterials that guide the biomedical and therapeutic domains for promoting the modern pharmaceutical industry. Many investigators had exploited such a potential technique to create/ameliorate numerous pharmaceutical carriers. These carriers show promising applications that vary from small drug to therapeutic protein delivery and from gene to living cell encapsulation design. Harmony between the properties of precisely engineered precursors and the formed network structure broadens the investigator's intellect for both brilliant creations and effective applications. As well, controlling photo-curing at the formulation level, through manipulating the absorption of light stimuli, photoinitiator system and photo-responsive precursor, facilitates the exploration of novel distinctive biomaterials. Discussion of utilizing different photo-curing procedures in designing/formulation of different pharmaceutical carriers is the main emphasis of this review. In addition, recent applications of these intelligent techniques in targeted, controlled, and sustained drug delivery with understanding of photo-irradiation concept and mechanism are illustrated.

Contents

1. Introduction

Photo-irradiation, which is the exposure to photo-energy out of the electromagnetic rays, has been utilized as a human activity since the earliest periods of our lives. The history of it can be traced back to the

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ancient Egyptians who used this technique in mummification [1]. The mummies have been wrapped in lavender oil soaked fabrics that turn into protective layers upon exposure to sunlight [1]. Since then, the photo-irradiation paradigm has grown up as a green chemistry tool for constructing biomaterials with variable configurations and structures [2–4]. Light is able to provide a sufficient energy for the irreversible conversion of liquid precursors to three dimensional structures (solid/gel networks) that can be utilized in different perspectives [5–7]. These perspectives have been expanded, nowadays, as a well accepted technology to implement material engineering concepts into applied biomedical research goals [2–4], including, but not limited to, the manufacture of dental filling materials, tissue regeneration supporting scaffolds and pharmaceutical vehicles for drug delivery [8–15]. Meanwhile, formulating pharmaceutical vehicles with this technique stimulates the creativity of researchers to prepare drug delivery systems that are smart enough to fulfill the desired medical purpose [3,6,7]. A schematic description for the photo-formulation of some pharmaceutical carriers is illustrated in Fig. 1A.

Among the accumulative formulation technologies, photo-irradiation has emerged as a promising approach due to the high curing speed, low energy input and low costs [11,16,17]. Controlling of its specifications can easily be manipulated to be tailored for a specific preparation condition [16–20]. Hence, precise control at pharmaceutical manufacture scale can be achieved [16,17,21,22]. Also controlling the

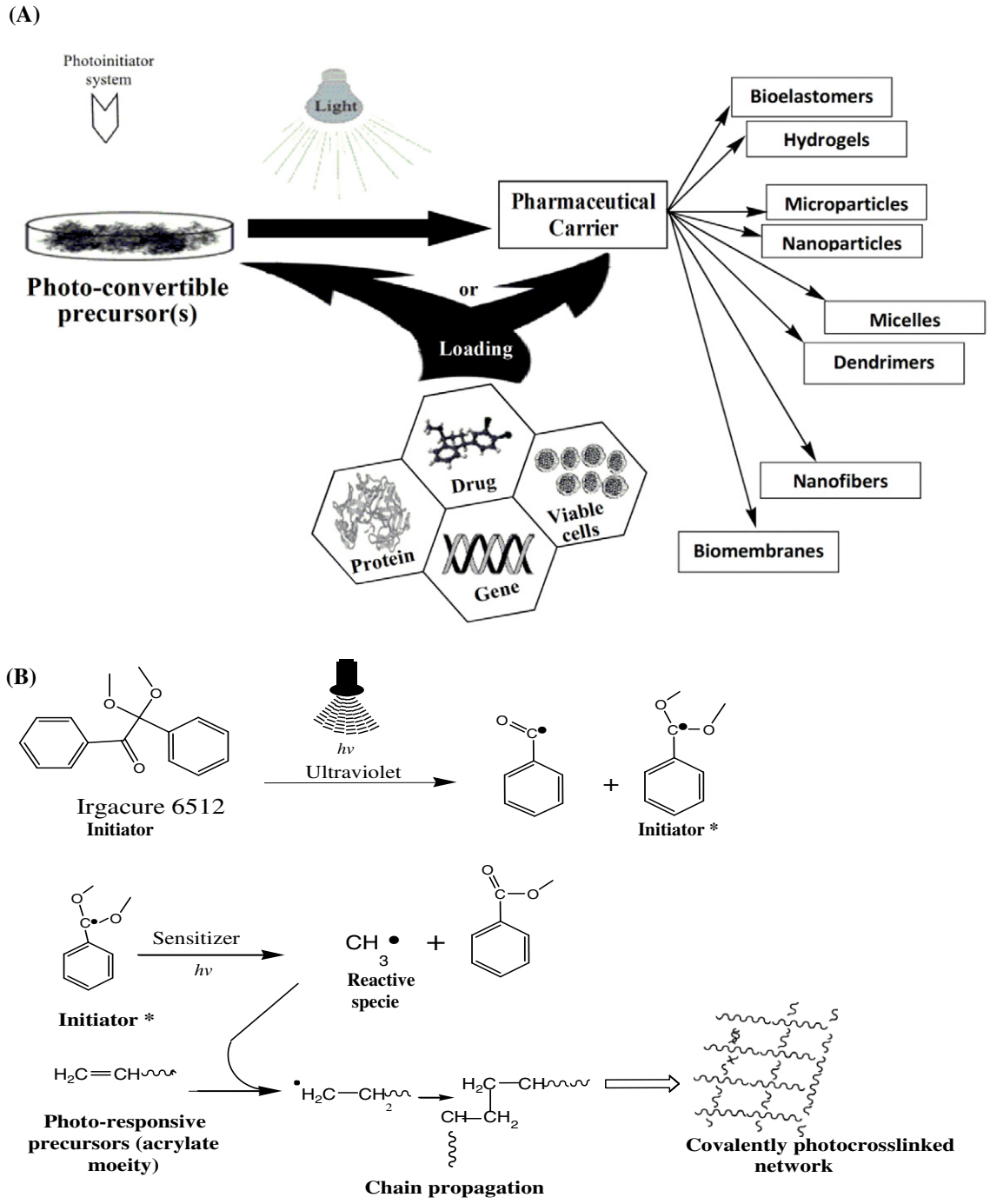
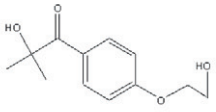
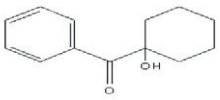
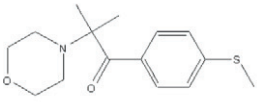
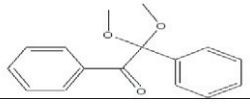
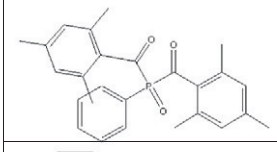
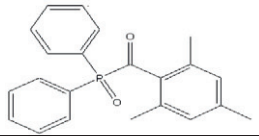
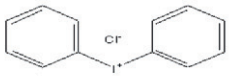
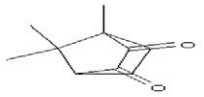
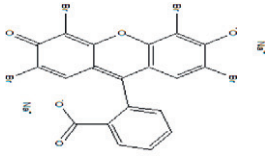
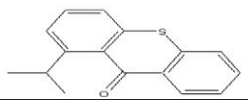


Fig. 1. (A) Overview scheme for the formulation of different pharmaceutical carriers using photo-irradiation. (B) Schematic representation for a radical generating photo-crosslinking through using ultraviolet as a photo-irradiation curing light, Irgacure 6512 (type I photoinitiator) and acrylated photo-responsive precursors.

Table 1
Selected examples for commonly used photoinitiators with their classes, structures, and cytotoxicity profile.

Class		Photoinitiator name	Type	Chemical structure	λ	Cytotoxicity profile*
Ultraviolet photoinitiators	Ketone	Irgacure 2959 2-Hydroxy-1-[4-(hydroxyl ethoxy) phenyl]- 2-methyl-1-propanone	Free radical (Type I)		276 nm	• Up to 0.05% (w/w) concentration after 48 h, shows 100% survival for fibroblast cells. • 0.1% (w/w) concentration after 48 h, shows 79% survival for fibroblast cells [1]
		Irgacure 184 1-Hydroxycyclohexyl-1-phenyl ketone			246 nm	0.03% (w/w) concentration after 48 h, shows only 38% survival for fibroblast cells [1]
		Irgacure 907 2-Methyl-1[4-(methylthio) phenyl]-2-morpholinopropan-1-one			230 nm	0.03% (w/w) concentration after 48 h, shows only 16% survival for fibroblast cells [1]
	Aceto-phenone	Irgacure 6512 2, 2-Dimethoxy-2-phenyl acetophenone (DMPA)			340 nm	0.02% (w/w) concentration after 48 h, shows only 32% survival for fibroblast cells [1]
	Phosphine oxide	Irgacure 819 Bis(2,4,6-trimethylbenzoyl) phenylphosphine oxide (BAPO)			295 nm	0.1% (w/w) concentration after 48 h, shows only 6.5% survival for fibroblast cells [2]
		Lucirin TPO Diphenyl(2,4,6-trimethylbenzoyl) phosphine oxide			295 nm	0.001% (w/w) concentration after 24 h, shows only 50% survival for lung cells [3]
	Iodonium salt	Diphenyliodonium chloride (DPIC)	Cationic		210 nm	0.16% (w/w) concentration after 24 h, shows 50% survival for fibroblast cells [4]
Visible light photoinitiators	Camphor derivative	Camphorquinone 1R,4S-1,7,7-trimethyl norbronane-2,3- dione	Free radical (Type II)		470 nm	0.01% (w/w) concentration after 48h, shows 61% survival for fibroblast cells [1]
	Dye	Eosin Y Disodium 2-(2,4,5,7-tetrabromo-6-oxido-3 -oxo-xanthen-9-yl) benzoate			510 nm	• 0.07% (w/w) concentration after 48 h, shows 88.4% survival for mesenchymal stem cells. • 0.7% (w/w) concentration after 48 h, shows 68.8% survival for mesenchymal stem cells [5]
	Photo-sensitizer	Isopropyl thioxanthone (ITX)			365 nm	0.05% (w/w) concentration after 48 h, shows 25% survival for fibroblast cells [1]

λ is the wavelength at which maximum spectral absorption of the photoinitiator occurred.
* result(s) of *in vitro* study, in which the viability of a selected cell line was measured after being incubated for a definite period of time with the photoinitiator at selected concentration.

wavelength, light intensity, duration of exposure, and beam diameter of incident light affords the spatial and temporal control to the *in situ* application. For example, appropriate selection of the light's wavelength significantly affects the extent of its curing effect. Irradiation in the ultraviolet (100–400 nm), visible (400–700 nm), and near infrared (700–2500 nm) regions can be clinically applied [3,20]. However, photo-energy from UV and visible light irradiation can be used only for topical purpose, due to the fact that, radiation below 700 nm cannot penetrate deeper than 1 cm into tissue. This limited penetration is commonly due to high scattering and absorption by blood component, mainly hemoglobin and water [18]. Nonetheless, near infrared light can penetrate at deep site of application (up to 10 cm into living tissue) since water absorbs wavelengths longer than 900 nm [16,19,20].

As a green chemistry tool, photo-irradiation can induce different types of synthesis/degradation reactions, however, the most commonly implemented reactions in pharmaceutical formulation are photo-reduction [23] and photo-polymerization [24–29]. The photo-polymerization is expressively enclosed in the creation of multi-functional, smart, reconfigurable, mechanized, and biomimetic pharmaceutical carriers [15,24–39]. Meanwhile, photo-irradiation as a flexible and facile polymerization technique enjoys several advantages over the conventional (thermal and solution) polymerization conditions. The high structural and

Table 2
Summary of selected examples from the reported photo-irradiated assemblages, demonstrating their application in drug delivery using various photo-cured biomaterials and photoinitiator systems.

Drug(s)	Photo-convertible precursor(s)	Carrier	Photoinitiator	Used light	Application
Propranolol HCl [2,94]	Poly(epsilon-caprolactone) oligomers functionalized with succinic anhydride	Bioelastomer	Camphorquinone	Visible light	Oral delivery of antihypertensive drugs
Papaverine HCl [92]	Acrylated poly(decane-co-tricarballylate)		Camphorquinone	Visible light	Potent vasodilator implant
Fluocinolone acetonide [64]	Poly(propylene fumarate)		NP	Blue dental curing light	Intra-ocular delivery of anti-inflammatory drugs
Doxorubicin HCl & protamine SO_4 [95]	Poly(propylene fumarate)		Irgacure 819	UV light	Implantable cancer chemotherapeutic device
Cyanocobalamin [96]	Poly(trimethylene carbonate) fumarate/methyacrylate		Irgacure 2959	UV light (250–450 nm)	Sustained delivery system for Vitamin B_{12}
Diflunisal [97]	Methacrylated/succinilated inulin	Hydrogels	NP	Short wave UV light (254 nm)	Controlled release system for non-steroidal anti inflammatory drugs
Doxorubicin HCl [98]	Acrylated pluronic F127 with poly(ethylene glycol) diacrylate		Eosin Y	Argon ion laser light (480–520 nm)	Long-term delivery for cancer chemotherapy
Thrombin [17]	Methacrylated hyaluronic acid & methacrylated α,β-poly(*N*-2-hydroxyethyl)-DL-aspartamide		NP	Long wave UV light (313 nm)	Hemorrhages management
Gentamicin So_4 [99]	Poly(ethylene glycol)diacrylate & hydroxyethyl methacrylate		Irgacure 6512	Long wave UV light (365 nm)	Controlled delivery system for antimicrobial drugs
Beclomethasone Dipropionate [77]	Methacrylated dextran and methacrylated α,β-poly(*N*-2-hydroxyethyl)-DL-aspartamide		NP	Long wave UV light (313 nm)	Targeted colon delivery for treating inflammatory bowel diseases
Paclitaxel [100]	Chitosan functionalized with both azide and lactose moieties		NP	UV light (240–380 nm)	Long-term delivery of anti cancer drug
Theophylline [47]	Glycidyl methacrylated dextran & glycidyl methacrylated α,β-poly(*N*-2-hydroxyethyl)-DL-aspartamide		NP	Long wave UV light (365 nm)	Oral drug delivery system
Diuron [101]	Carboxymethyl chitosan-azidobenzaldehyde		NP	Short wave UV light (253.7 nm)	Controlled delivery of pesticides
Fluorescein isothiocyanate– dextran [31]	Silk fibroin & poly(vinyl alcohol) methacrylate		Irgacure 2959	Long wave UV light (365 nm)	Delivery system for macromolecular drugs
Ibuprofen [13]	Dextran methacrylate	Solid lipid nanoparticles in hydrogels	NP	Long wave UV light (310 nm)	Controlled release system for non-steroidal anti inflammatory drugs
Doxorubicin HCl [102]	CaF_2:Ce^{3+}/Tb^{3+}-polyacrylic acid	Hollow microspheres	Lucirin TPO &N,N′ methylene bisacrylamide	UV light	pH responsive targeted delivery for anti cancer drugs
Rivastigmine [8]	Poly(hydroxyethyl) methacrylate & poly(hydroxyethyl) methacrylate-poly(ethylene glycol)	Nanoparticles	NP	Short wave UV light (254 nm)	Delivery system for Alzheimer's treatment
6-Mercaptopurine [23]	Chloroauric acid		NP	Sun light	Targeted anticancer delivery to treat laryngeal cancer
Tamoxifen citrate [41]	Poly(ε-caprolactone fumarate)	Liquid injectable gel system	Camphorquinone & dimethyl-p-toluidine	Visible light	*In situ* forming implant for breast cancer treatment
Timolol maleate & sodium flurbiprofen [11]	Starch isocyanatoethyl methacrylate	Thin film	Irgacure 2959	UV light	Ophthalmic delivery system for glaucoma treatment
Vancomycin [103]	Acrylated poly(ethylene glycol)		Irgacure 6512	Long wave UV light (365 nm)	Protective tactic from orthopedics infections
Proxyphylline [104]	Oligo (ethylene glycol) multiacrylates & acrylic acid		Irgacure 6512	UV light	Sustained drug delivery
Ofloxacin [6]	Poly(ethylene glycol)-co-poly(glycolic acid)-co-methacrylate & polyamidoamine-metharylamide	Denderimers	a,a-Diethoxy acetonphenone	Short wave UV light (254 nm)	Controlled drug delivery
Quercetin [105]	Acrylated polycaprolactone poly(ethylene glycol) & ethylene glycol dimethacrylate	Micelles	Irgacure 2959	UV light	Targeted delivery for cancer therapy
Doxorubicin HCl [66]	Poly(ethylene glycol)-poly(aspartate-hydrazide-cinnamate)		NP	UV light	Controlled delivery for cancer chemotherapy
Farodiol esters (*Calendula officinalis* extracts) [106]	Hyperbranched polyglycerol methacrylate	Nanofibers	NP	Short wave UV light (280 nm)	Dressing for wound healing
Nicotinamide [107]	Poly(acrylic acid) & poly(hydroxyethyl methacrylate)	Biomembrane	Irgacure 819	UV light	pH responsive delivery system for Vitamin B_3
Methylene blue [108]	Hydroxy ethyl methacrylate & mixture of acrylic acid, N-isopropyl acrylamide, polyethylene glycol dimethacrylate and photo-responsive prepolymer		Irgacure 819 ± 2-hydroxy-2-methyl-1-phenylpropane	UV light	Stimuli responsive delivery device to treat methemoglobinemia and urinary tract infections
Nicotinic acid [107]	Poly(acrylic acid) & poly(hydroxyethyl methacrylate)		Irgacure 819	UV light	pH responsive delivery device for antihyperlipidemic drugs
Caffeine [109]	Poly(acrylic acid) or acrylic acid/2-(diethylamino) ethyl methacrylate & poly(hydroxyethyl methacrylate)		Irgacure 819	UV light	pH responsive delivery for caffeine.
Nicotine [110]	Hydroxyethyl methacrylate and mixture of acrylic acid, polyethyleneglycol dimethacrylate and photo-responsive prepolymer	Biomembrane	Irgacure 819	UV light	Glucose-responsive nicotine release membrane for smoking secession
Ondansetron [93]	Dextran and N-isopropylacrylamide		NP	Gamma-ray	Thermo-sensitive antiemetic delivery system to treat nausea and vomiting following chemotherapy

NP = no photoinitiator used.

Table 3
Summary of selected examples from the reported photo-irradiated assemblages, demonstrating their application in proteins/peptides delivery using various photo-cured biomaterials and photoinitiator systems.

Protein(s)/peptide(s)	Photo-convertible precursor(s)	Carrier	Photoinitiator	Used light	Application
Vascular endothelial growth factor ($VEGF_{165}$) & hepatocyte growth factor [111]	Acrylated star poly(trimethylene carbonate-co-ε-caprolactone-co-D,L-lactide)	Bioelastomer	Irgacure 6512	Long wave UV light (320–480 nm)	Treatment for chronic myocardial and peripheral ischemia
Interferon-γ [112]	Acrylated star poly(ε-caprolactone-co-D,L-lactide)		Irgacure 6512	Long wave UV light	Controlled delivery device for cancer immunotherapy
Interleukin-2 [91]	Acrylated poly(decane-co-tricarballylate)		Camphorquinone	Visible light	Controlled delivery for cancer immunotherapy
Bovine serum albumin & horseradish peroxidase [113]	Poly(ethylene glycol) diacrylate & alloplastic materials derived from poly(methylmethacrylate)		Camphorquinone	Visible blue light (420–500 nm)	Bone tissue repair and regeneration
Peptide fragment of serum amyloid A (MFFD) [10]	α,ω-Diacrylate oligo(D,L-lactide)-b-poly(ethylene glycol)-b-oligo(D,L-lactide) & ω,ω,ω-triacrylate star poly(ε-caprolactone-co-D,L-lactide)		Irgacure 6512	Long wave UV light (320–380 nm)	Anti-atherosclerotic peptide delivery system
Recombinant human bone morphogenetic protein-2 [43]	Poly(propylene fumarate)	Microspheres embedded in bioelastomeric rod inside a hydrogels	Irgacure 819	UV light	Bone regeneration
Bone morphogenetic protein-6 & transforming growth factor-β_3 [114]	RGD-grafted N-methacrylate glycol chitosan	Microspheres embedded in hydrogels	Irgacure 2959	Long wave UV light (320–480 nm)	Augmentation for the chondrogenic differentiation of encapsulated stem cell
Human insulin [115]	Poly(methacrylic acid-g-ethylene glycol)	Microparticles embedded in hydrogels	Irgacure 6512	Long wave UV light (365 nm)	Oral insulin delivery for treating type 1and 2 diabetes
Salmon calcitonin [116]	Poly(methacrylic acid-g-ethylene glycol)	Thin film	Irgacure 184	UV light	Oral calcitonin delivery for treating osteoporosis
Recombinant human basic fibroblast growth factor [117]	Chitosan functionalized with both azide and lactose moieties	Hydrogels	NP	Long wave UV light (240–380 nm)	Occlusive dressing for wound management
Silk fibroin protein (isolated from *Bombyx mori* silkworm cocoons) [31]	Poly(vinyl alcohol) methacrylate		Irgacure 2959	Long wave UV light (365 nm)	Hybrid delivery system for macromolecular drugs
Bovine serum albumin [34]	N-isopropylacrylamide, poly(ethylene glycol)-co-poly(epsilon-caprolactone) & sodium alginate		Irgacure 6512	Long wave UV light (365 nm)	Delivery system for protein and peptide
Horseradish peroxidase & bovine serum albumin labeled with fluorescein isothiocyanate [118]	Sebacic acid dimethacrylate, 1,6-bis-carboxyphenoxyhexane dimethacrylate & poly(ethylene glycol) diacrylate	Microparticles	Camphorquinone & ethyl 4-N,N-dimethylamino-benzoate	Blue dental curing light	Injectable delivery system for long-term delivery of therapeutic protein
Vascular endothelial growth factor (VEGF) & Bone morphogenetic protein-2 [44]	Poly(ethylene glycol)–calmodulin–poly(ethylene glycol)	Microspheres	Irgacure 2959	Long wave UV light (365 nm)	Bone tissue and wound repair
Bovine serum albumin [119]	Poly(ethylene glycol)diacrylate	Nanoparticles	Irgacure 2959	UV light	Thermo-responsive protein delivery system
Salmon calcitonin [120]	Poly(methacrylic acid-g-ethylene glycol)	Nanospheres	Irgacure 184	UV light	Oral calcitonin delivery for treating osteoporosis

NP = no photoinitiator used.

Table 4
Summary of representative examples from the reported photo-irradiated assemblages, demonstrating their efficacy for delivery of immunotherapeutic proteins using various photo-cured biomaterials and photoinitiator systems.

Protein(s)	Photo-convertible precursor(s)	Carrier	Photoinitiator	Used light	Application
Immunoglobulin G (IgG) [121]	Inulin functionalized with methacrylic anhydride/succinic anhydride & α,β-poly[N-(2-hydroxyethyl)-D,L-aspartamide] methacrylic anhydride	Hydrogels	NP	Long wave UV light (366 nm)	Targeted colon delivery system for human IgG
Bacterial vaccine (*Brucella abortus*) [122]	Methacrylated poly(ethylene glycol), methacrylated poly(ethylene glycol)-co-glycolide & methacrylated poly(ethylene glycol)-co-lactide	Microspheres embedded in hydrogels	Irgacure 184	UV light	Biobullets delivery vehicle for vaccines to be fired intramuscularly
Goat anti-mouse IgG antibodies [123]	Polyethylene glycol diacrylate & GFLGK peptide diacrylate	Nanoparticles	Irgacure 2959	Long wave UV light (365 nm)	Controlled enzyme-triggered delivery of antibodies
Streptavidin-CY5 [123]					Disease-controlled delivery of biomacromolecules

NP = no photoinitiator used.

Table 5
Summary of representative examples from the reported photo-irradiated assemblages, demonstrating their efficacy for gene delivery using various photo-cured biomaterials and photoinitiator systems.

Gene	Photo-convertible precursor(s)	Carrier	Photoinitiator	Used light	Application
DNA plasmid [73]	Diacrylated pluronic F127 ± methacrylated hyaluronic acid	Hydrogels	Ouantacure	Long wavelength UV light	Sustained gene delivery
siRNA [124]	Methacrylated dextran & methacrylated linear ethyleneimine		Irgacure 2959	Long wavelength UV light (320–500 nm)	Gene therapy and regenerative medicine applications
DNA plasmid [125]	Acrylated hyaluronic acid & a 4-arm acrylated polyethylene glycol		Irgacure 2959	Long wavelength UV light (365 nm)	Controlled gene delivery
DNA plasmid [123]	Polyethylene glycol diacrylate with GFLGK peptide diacrylate	Nanoparticles	Irgacure 2959	UV light (365 nm)	Disease-controlled gene delivery

Table 6
Summary of selected examples from the reported photo-irradiated assemblages, demonstrating their efficacy for viable cells delivery using various photo-cured biomaterials and photoinitiator systems.

Cell(s)	Photo-convertible precursor(s)	Carrier	Photoinitiator	Used light	Application
Human mesenchymal stem cells [38]	Pentaerythritol triacrylate & poly(trimethylene carbonate)	Bioelastomer	Irgacure 369	Short wave UV light (254 nm)	Regenerative medicine applications
Bovine coronary artery smooth muscle cells [21]	ω,ω,ω-Triacrylate [star poly(ε-caprolactone-co-D,L-lactide)] acrylloyl-polyethylene glycol conjugated with GRGDS peptide		Irgacure 6512	Long-wave UV light	Smooth muscle regeneration for vascular grafts
Goat mesenchymal stem cells [82]	Acrylated poly(6-aminohexyl propylene phosphate)	Hydrogels	Irgacure 2959	Long-wavelength UV light (365 nm)	Bone tissue regenerative applications
Insulin-secreting pancreatic β-cells (MIN6) [126]	4-arm polyethylene glycol-norbornene & polyethylene glycol diacrylate		Lithium arylphosphanate	Long-wavelength UV light (365 nm)	Pancreatic β-cells regeneration for type 1 diabetes
Hepatocytes with fibroblast cells (NIH 3T3-J2) [127]	Polyethylene glycol diacrylate		Irgacure 2959	Long-wavelength UV light (365 nm)	Hepatic tissue regeneration
Adipose-derived stem Cells [114]	RGD-grafted N-methacrylate glycol chitosan		Irgacure 2959	Long wave UV light (320–480 nm)	Focal chondral repair
Fibroblasts (NIH-3T3) [81]	Gellan gum methacrylate & gelatin methacrylamide		Irgacure 2959	Long wave UV light (320–500 nm)	Regeneration of load-bearing tissues
Neural progenitor cells [128]	Hyaluronic acid methacrylate		Irgacure 2959	Long wave UV light (365 nm)	Regeneration of dopaminergic neurons of the substantia nigra cells for treating Parkinson's disease
Fibroblasts (L929) [129]	Polyvinyl alcohol	Microspheres	Irgacure 2959	Long-wavelength UV light (300–500 nm)	Immunoisolated cell delivery vehicle
Insulin-secreting porcine islets of Langerhans [130]	Polyethylene glycol diacrylates		Eosin Y & triethanolamine	Argon ion laser light	Immune protection for allo- and xeno-transplantation of islets of Langerhans
Bovine articular chondrocytes [131]	Methacrylated hayllouronic acid & *N*-vinylpyrrolidone	Beads	Ouantacure	Long-wavelength UV light	Implantable/injectable cell delivery vehicles for cartilage regeneration
Human bone marrow stromal cells [132]	Pectin & diphenylamine-4-diazoresin	Thin film	NP	Long-wavelength UV light (350 nm)	Regenerative medicine applications

NP = no photoinitiator used.

chemical variability of polymers that can be created by this synthesis approach employed to construct a diversity of biomimetic materials [24–39]. The ability to manipulate the polymerization condition in response to a certain irradiation conditions, attracts great research attention for implementing it in resolving insuperable biomedical problems [3,40]. Moreover, it can be appropriately applied for *in situ* formulation, with extremely high precision and manageability [3] This *in situ* photo-formulation is successfully used for implantation purpose as it constitutes biomaterials that adhere and conform to the localized tissue, in a minimally invasive manner [18,41–43].

With the aforementioned reputations, photo-irradiation paradigm has been exploited in the development of recent pharmaceutical delivery systems. It also integrates the numerous formulation ideas with the aim of achieving less industrial hazards and optimizing clinical outcome of drugs. Hence, this review emphasizes the different means of optimizing the photo-irradiation in designed delivery system including understanding of its mechanistic action, defining its potentials and challenges, and relating all this knowledge to the strategies used in the formulation of different pharmaceutical carriers.

2. Photo-irradiation mechanism

Photo-irradiation is a straightforward process induced by the absorption of light stimuli (as a non ionizing radiation energy) that elevates the reactant molecule's energy to a level required for chemical changes [38,44]. This absorbed energy is sufficiently enough to either initiate/propagate chemical reaction or conduct crosslinking action [45]. Accordingly, integrated photo-irradiation assemblage is composed of light source, photoinitiator system (PIS) and photoresponsive precursor (PRP). Light represents a source of electromagnetic waves that travel in the form of photo-waves/particles and carry radiant energy [38,44,45]. PIS acts like a recipient for this photon energy from a selective wavelength light [46,47] and conducts a quick chemical transformation to the PRP, mainly through electronic excitation [38,44,45].

2.1. Photoinitiator system

PIS comprises one or more of photoinitator (PI) alone or in combination with catalysts (synergetic molecules such as photosensitizers and photoaccelerators). PI initiates the photoreaction through the generation of reactive species (mostly free radical), once exposed to appropriate light [3,48]. These reactive species attack the photosensitive moiety of PRP (mostly the double bond). Then this reacted precursor sequentially reacts again with another new PRP and proceeds with chain propagation till the completions of the photo-polymerization/crosslinking process. A schematic representation for an example of photo-irradiation is illustrated in Fig. 1B. Some PI cannot perform those steps alone and needs co-initiator (sensitizer/accelerator). Photosensitizer is capable of absorbing light energy and works either directly with PI or through transferring the photo-energy to PI [3,16], while, photoaccelerator acts only to speed up the PI action [40,49–51].

Three distinct classification systems have been established to categorize PIs. The first one is according to the type of reactive species generated after PI being irradiated, where they are classified into anionic, cationic, and free radical [52,53]. Anionic PIs liberate an anionic nucleophilic product and used for anionically initiated photoprecursors (*e.g.* acrylates) [46]. Cationic PIs produce cations (such as Brönsted or Lewis acid) that work upon cationically photoreactive molecules (*e.g.* epoxies) or molecules which undergo photo-crosslinking through polycondensation reactions [52]. Cationic photoinitiator was found to be ineffective in biological systems, since its reactivity is certainly inhibited by water [52], whereas free radical liberating PIs are water compatible and suitable for *in situ* formulation and viable cell encapsulation [53]. Accordingly free radical PI is the commonly used one in pharmaceutical carriers' formulation. Table 1 lists some examples for commonly used

PIs with their class, type, chemical names, structures and cytotoxicity profiles.

The second classification is according to the initiation mechanism in which free radical PIs are divided into two general classes. The first (type I) undergoes a uni-molecular bond cleavage upon irradiation to yield free radicals, as illustrated in Fig. 1B [52,54]. Meaning that PI alone initiates the photo-formulation without co-initiator. The majority of this type includes aromatic carbonyl compounds containing suitable groups which facilitate direct photofragmentation [54], whereas, the second (type II) is subjected to bimolecular reaction, where the excited PI interacts with photosensitizer (by hydrogen abstraction mechanism) to generate the free radical [46,53]. Meaning that PI alone cannot initiate the photo-formulation and photosensitizer is deemed required with PI.

The third classification system is according to the type of light used to induce photoinitiation where PIs have also been categorized into ultraviolet (UV), visible and laser PIs [46,55,56]. The only dissimilarity between them is the difference in the appropriate light wavelength range where absorption capability of the PIs occurs. The UV PIs in turn include various classes (Table 1).

The preceding discussion illustrates PIs as chemical compounds work through the generation of biologically harming species, that may pose a considerable toxicity. So some investigators evaluated their biological damage through cytotoxicity studies on selected cell lines, with the aim of investigating the extent of toxicity and cytocompatible dose for each PI (Table 1) [57–61]. Therefore the ultimate selection or preference of any PIS is principally based upon the reported assemblage with the highest cytocompatibility in the literature *e.g.* Irgacure 2959 [58]. At the same time a good PIS should provide the following: complete stability *i.e.* does not initiate spontaneous reaction when mixed with the photoreactive molecules [62]; shows a rapid and high initiation efficacy to maximize utilization of undissociated PI that degrades the quality of the formulated pharmaceutical carrier [56]; and appropriate with the incorporation of proteins/peptides or the encapsulation of viable cells [56]. Also, it cannot be overlooked here that some delivery carriers can be photo-formulated without using a PI, instead they depend on long time exposure of the photo-responsive molecules to the light energy, such as the formulation using inulin-methacrylic anhydride [15] and methacrylated dextran [47] which can be photo-crosslinked only by UV-irradiation for 4 and 6 h, respectively.

2.2. Photo-responsive precursors

The concept of photo-responsive (photo-convertible) precursor is being employed for macromolecules having at least one photosensitive moiety in their structures, which usually locates at one or both of their ends. This moiety contains domain bond (almost double bond or epoxide) that is irreversibly changed by irradiation in the presence of PIS. Acrylates [63], methacrylates [13], and cyano-acrylates [46] are commonly used photosensitive moieties, that can be covalently crosslinked with the excitation of free radical generating PIs. Similarly, fumarate moiety which is commonly used for the formulation of different injectable/implantable biomaterials is covalently crosslinked upon exposure to photo-irradiation [64]. Also the thiolene moiety functional systems are working through the excitation of free radicals, but, proceed through step-growth mechanism [65], whereas cinnamate [62,66] and anthracene [67] moieties undergo reversible photodimerization upon light irradiation. Less commonly used moieties are epoxidized moiety that forms ether bridges in the presence of iodonium salt as a PI [68] and the styrylpyridinium moiety which undergoes cycloaddition reactions upon exposure to photo-irradiation [69]. Tables 2–6 show selected examples for photo-responsive biomaterials built with the conjugation with one or more of photo-convertible moieties and have been formulated as pharmaceutical delivery matrices. These tables also illustrate their applications for delivery of various drugs, peptides, genes and viable cells, separately.

For instance, polyvinyl alcohol (PVA) has been widely explored as a photo-formulated vehicles (Tables 2, 3 and 6), due to its distinguished characteristics. First, it represents an excellent protein non-adhesive biomaterial that clarifies its potential for candidacy as a protein-releasing matrix [31]. Second, the number of crosslinkable groups on the PVA chain can be widely varied, permitting greater manipulation of mechanical properties [25,31,32]. Third, the pendant hydroxyl groups on PVA provide more available sites for the attachment of bioactive molecules [31,32]. Jennifer et al. explored the application of photo-irradiated PVA derivatives in supporting viable cell delivery by binding it with RGD-containing peptide (Arg–Gly–Asp) [70]. Polyethylene glycol (PEG) as another example has been shown excellent photo-crosslinking through its conjugation with a photosensitive moiety such as acrylate, methacrylate or fumarate derivatives (Tables 2–6) [71,72]. As such PEG urethane-dimethacrylates have showed good biocompatibility and have been successfully used by several investigators in viable cell delivery [71,72]. Chun et al. explored the thermal gelling character of UV-irradiated PEG/polypropylene oxide co-polymer as well as its candidacy for use as delivery systems for several genes and proteins including interleukin-2 (IL-2), urease, and intestinal natriuretic factor [35,73]. Likewise polyhydroxyethyl methacrylate [74] and polyglycerol methacrylate–glycidyl methacrylate [75] showed great potential as a carrier due to their biocompatibility and ability to sustain the release of entrapped pharmaceuticals.

Naturally occurring materials, whose degradability inside the body is well known, such as starch [76], dextran [77], inulin [78], collagen [18], chitosan [79], hyaluronic acid [80], gelatin [81], alginate [48], and polyphosphester [82] also have been included in different photo-formulated pharmaceutical carriers (Tables 2–6). Among those natural macromolecules, polysaccharides represent good candidates to prepare bioerodible vehicles [17,83]. Polysaccharides are readily available and can be homogenously and consistently degraded by hydrolysis [83,84]. Besides their compatibility and biodegradability, they possess hydroxyl groups that can smartly be used for the covalent attachment of drugs [83,84]. Several researchers have demonstrated the drug release profiles for photo-irradiated polysaccharide matrices. Dextran is a reputable natural polysaccharide that is widely used in the pharmaceutical field, as such; photo-cured dextran derivative containing methacrylate moieties represents a simple and reproducible procedure to obtain networks able to swell in aqueous medium to form a soft bioerodible matrix [77,85].

It is worthy to mention the tricky selection/preference for any of the literally reported PRP firstly based upon the toxicity of the conjugated photo-responsive moiety as well as the deemed characteristics of used precursors to be established in the obtained pharmaceutical carrier. Toxicity of PRP has been examined in some *in vitro*/*in vivo* studies, however, the cellular mechanism of the reported toxicity is not clear yet [86,87]. These studies revealed that the photosensitive moiety reduced the cellular level of glutathione and increased the level of reactive oxygen species which cause DNA damage and apoptosis to exposed cells [86–89]. Nonetheless, other studies done on PRP after photo-irradiation have pointed out that the photo-reacted PRP shows a minimal or no significant toxicity compared to un-reacted PRP [88,90]. This minimal toxicity is basically dependent on the amount of PRP left un-reacted after photo-irradiation process [88,90]. Secondly, the consistency between the deemed PRP characteristics (such as usability, biodegradability, mechanical elasticity, and architecture adaptability) is essential in the selection and for the success of obtained pharmaceutical carrier. As such, the mechanical elasticity of the PRP, which relies on crystalline pattern and crosslinking density, is reflecting the lifetimes of the obtained biodegradable carrier [3,91]. The architecture of the PRP, which is based mainly on the nature of the backbone structure and the type/concentration of the building unit, affects the biodegradation mechanism that might occur by merely bulk erosion, surface erosion or a combination between them [63,92].

2.3. Used light

Several light sources have been practically explored for the photo-formulation including ultraviolet (UV) lamps, visible light lamps, plasma arc lamps, light emitted diode, titanium-sapphire laser, and gamma irradiator [16,19,20,46,53,93]. The main differences associated with those sources are the generated light wavelength, intensity and the associated amount of entropy loss (heat evolved) [53]. Nonetheless, the irradiation with direct sun light (during the noon time) was also employed in photo-formulation [23].

Mathematically, the quantity of light energy deemed for running photo-irradiation process depends mainly on the emission intensity of the used light source (irradiance), irradiated area from the assemblage system, as well as the irradiation time. The irradiance (E, measured in Watts/cm^2) is calculated from the brightness of used light (I, measured in Watts) and the distance from the light source to the assemblage system (r) [$E = I / r^2$]. Here, brightness could be calculated based on the light power (Φ, measured in Watts) and the solid angle (Ω) [$I = \Phi / \Omega$]. Likely, this solid angle is calculated from the area (A) and radius (r) of the used light bulb [$\Omega = A / r^2$] [16,19,20,46].

As light absorption through the PIS is often described by Beer Lambert law, tuning between excitation wavelength of light source and the spectral absorption of PI has an ultimate curing effect on PRP. Consequently light parameters (spectrum, intensity and irradiation time) directly influence the success of formulating pharmaceutical vehicles and indirectly influence the residual share of un-reacted toxic constituents [4,50]. The alliance between the used light and the photo-formulation success was investigated in a number of studies [4,50,62,133,134]. It has been revealed from such studies that the degree of curing depends on the power density and the exposure duration. At power densities of 20–300 mW/cm^2 and exposure durations between 1 and 30 min they observed the least un-reacted content and highest mechanical strength [4,50,62,133,134]. Meanwhile, some other researchers have endorsing attempts to minimize the calculated dose of light (period of light exposure) and the upper intensity limit for the used source, to limit the light intensity dependent and inevitable heat increment as well as deactivation/decomposition of sensitive bioactive molecules [63,92]. For instance, the use of high intensity and long-wave UV radiation could have greatly accelerated therapeutic protein oxidation and denaturation, in comparison with low intensity radiation or visible light photo-irradiation.

3. Photo-irradiation biocompatibility

In view of how photo-irradiation occurs, the following questions will come to mind: Wouldn't this reactive molecule mechanism of the PI be associated with great clinical challenges (toxicity and tissues damage)? Do we need comprehensive cytocompatibility and biocompatibility studies for the formulated photo-irradiated biomaterial before clinical trial? An essential prerequisite to qualify the formulation technique/formulated carrier as accepted delivery strategy is biocompatibility, which is the ability to perform its desired function with an appropriate host response. Although several studies about the applications and the superiority of the photo-formulation in the preparation of various pharmaceutical carrier have been explored, little has been described the biocompatibility of this technique and/or those formulated carriers, as an obstacle against the full clinical application.

From mechanism sight, it can be revealed that the possible factors influencing biocompatibility of photo-formulation process can be confined in the following: first, suitability of the used light source and generated heat during application; second, the toxicity profile of PI and the generated reactive species from it [3]; and third, the considered damaging nature for the released un-reacted PRP after the delivery vehicles is administered [89]. In particular, un-reacted acrylated moieties are primarily harmful to health when released inside the human body [87]. For example, it is found that the percentage of the un-reacted double bonds in the photo-irradiation of acrylated PRP varies from 20% to 65% [89]. These un-reacted PRP should be avoided/minimized for improving the biocompatibility. Therefore, the current challenge facing the clinical applications of the photo-formulated delivery system has been explored in achieving two major concurrent goals. The first is optimizing the preparation conditions to the extent of ensuring that PIS and PRP are fully converted to the required networks/matrices to improve the carrier performance and optimize its biocompatibility. The other one is maintaining the stability and activity of loaded candidate molecules (drugs, proteins, genes or viable cells) during the irradiation through the appropriate selection of safe constituent and friendly light source and power. Work on this challenge is still ongoing.

Consequently every photo-irradiation assemblage, intended for final development into a biomedical device or a pharmaceutical carrier, must undergo comprehensive toxicity testing for its component as well as rigorous biocompatibility assessment and optimization [2,5]. Description for the different testing protocols and evaluation approaches has recently been reviewed and the reader is strongly advised to refer to those reviews [3,135]. Usually this examination goes ascendingly from *in vitro* cell toxicity investigation (short term contact with appropriate cell line), to *in vivo* living tissue friendly interaction proof [55,63]. At the *in vitro* level, each of the components must demonstrate the ability to work without causing adverse effects on the surrounding cell viability and proliferation ability. Although the choice of the relevant cell line is still controversial, phenotypical normal cells are most commonly selected as a useful model system because of their high sensitivity during proliferation [4,66,135,136]. In the same manner, the *in vivo* assessment of tissue compatibility in animals indicates the adverse tissue response, determines the host response and detects the host and identifies the possible source of damage that might accompany the *in situ* application [2,55].

It is worth mentioning that the exposure of normal healthy cells/tissues to generated reactive species (mostly free radical) has been associated with variable physiological and pathological events [82,137]. Nonetheless, several scientists are arguing that the presence of PRP in the assemblage is sufficiently enough to prevent that damage as they act as scavengers for those reactive species [4,135]. Meanwhile, healthy cells are able to surmount from such exposures through different cellular consequences and protecting antioxidant systems. That exposure recovery fluctuates according to the nature of the generated reactive species, their intra/extra-cellular location, and the biological structure and function of the exposed cells [66,70]. Nevertheless, the presence of any kind of significant toxicity or tissue damage should promote the investigator to modify the formulation accordingly to achieve the needed level of biocompatibility, for example, through changing the PI type/dose or the used light source/intensity.

Another parameter that might have an impact on biocompatibility is the immunogenicity of the obtained vehicles. Stimulation of immune-reaction can potentially cause the failure of implantable carrier with usage trial. Therefore, accurate investigations of immuno-compatibility can be done through a broad screening for all the proposed source of immunogenicity *i.e.*, *in vivo* immuno-acceptance testing with appropriately selected host in the specified implant site. When such a vehicle is settled, synergy with surrounding living tissue occurs and results in biological/immunological responses that appear at both the gross level and the microscopic level. This host action is influenced by a number of factors related mainly to the nature of the obtained biomaterial (such as surface topography, charge, and chemistry) and the properties of the body part where the assemblage administered (including tissue type, local pH and blood perfusion rate) [138,139].

Finally, the clinical assessment for the full biological response through the usage test is a crucial step and represents the most relevant test for biocompatibility evaluation and both *in vitro* and *in vivo* testing are measured as a tentative trial for its relevance [139]. On the other hand, approbation as a concern for biocompatibility with each of the utilized photo-irradiation technique can be confined in two domains: the

overall patient's health safety and practitioner's health safety. Avoid harming the patient is the primary concern during photo-irradiation application through appropriate use of the technique [139]. At the same time practitioner is to be cautious of potential harmful effects from the cumulative light exposure. UV blocking spectacles and face shields provide eye and face protection. Also, warning signs for the presence of light equipment should be visualized in the practice place [138].

4. Photo-cured pharmaceutical carriers

During last decades, different photo-cured pharmaceutical carriers and delivery strategies have been explored in recent biomedical and pharmaceutical application, trying to fulfill two main purposes. The first is the safe, targeted delivery of the drug to its site of action, to improve drug pharmacokinetics and the way drug is administered (maximize its therapeutic efficacy and minimizing its unwanted side effects). The second is to maintain the stability of loaded bioactive molecule and overcome biocompatibility issues during formulation and post-administration to the body. Early photo-formulation studies focused mainly on achieving a localized and/or sustained/controlled release to increase the therapeutic outcome; with extending drug plasma half-life and decreasing the drug amount to which other non-intended tissues are exposed upon administering. Current photo-cured carriers that concern how efficient the methods and strategies used to photo-formulate pharmaceuticals, to achieve the two mentioned purposes, are running in parallel with efforts to use them in the treatment of different diseases. More particularly, these photo-formulated carriers include bioelastomers, hydrogels, micelles, dendrimers, biomembranes as well as micro/nanocarriers (Fig. 1A). With each of them photo-irradiation strategies were done either during the formulation (*i.e.*, one or more PRPs are used and the photo-irradiation step is crucial for the carrier formation) or post formulation (*i.e.*, modify, functionalize, stabilize, fortify, or strengthen the already formulated carrier). Here, in this discussion we present the development of each of the aforementioned pharmaceutical carriers with a focus on some of the primary benefits that have established each of them in the development of drug delivery system and the method of drug administration. Concurrently, Tables 2–6 list more summative details regarding conducted researches done in various delivery systems with their allocated applications including the delivery of drugs, proteins/peptides, genes, and viable cells. It is important to state here that the used references are only representative citations for research work conducted on those photo-formulated delivery systems and do not constitute a comprehensive list of all the work done in that area.

4.1. Bioelastomers

With the rationale of being formulated easily and rapidly, photo-cured bioelastomers gained particular attention as depots for thermosensitive bioactive molecules. They were broadly used as biodegradable implant for the following features they own: the exhibition of mechanical properties being as soft as body tissues makes them attractive for the implantation in the highly challenging nonstatic parts of the body; their elasticity can be utilized along with osmotic potential to generate linear release profiles for water soluble compounds in protein/peptide delivery [112,140]. In addition, the availability of tuning the mechanical and biodegradation characteristics through the selection of appropriate photo-crosslinkable precursors. Lifetimes of such bioabsorbable implants could be adapted by adjusting the molecular weight, degree of crystallinity and crosslinking density of the engineered photo-cured matrices [112]. Moreover, the photo-irradiated elastomers with precisely engineered building units and friendly formulation conditions exemplify ideal carriers for viable cell encapsulation [21,38] and prolonged delivery of cytokines [91,140,141] (Tables 3 and 6). There are many PRPs that had been implied to prepare bioelastomers such as peptide conjugated acryloyl polyethylene glycol [21], cinnamated poly(glycerol sebacate) [29,62], methacrylated star poly(ε-caprolactone-co-D,L-lactide) [142], poly(ε-caprolactone-co-trimethylene carbonate) [143], poly(ε-caprolactone) end-functionalized with maleic or itaconic anhydride [144], poly(ε-caprolactone) chain extended with 4,4(adipoyldioxy) dicinnamic acid [145], and poly(ε-caprolactone) combined with polyethyl acrylate [146].

Many researchers exploited these potential advantages for the delivery of various drugs and proteins. For example, Younes et al. used photo-crosslinked bioelastomeric implants for bioactive protein delivery in localized cancer immunotherapy [112]. Biodegradable elastomeric matrices loaded with interferon-γ, vascular endothelial growth factor and IL-2 have been investigated and reported lately for their suitability as sustained release carrier [112,140]. These devices were formulated through UV-irradiation of an acrylated star poly(ε-caprolactone-co-D,L-lactide). The sustained release profile was achieved by incorporating the protein as lyophilized particles within the matrix (before photo-irradiation) and relied on the osmotic activity of the enclosed excipients (*e.g.* trehalose) to drive the protein release out of the elastomer. In this study, they chose a star shape PRP architecture since the physical properties of the final network can be easily altered on the basis of the number of arms of the star shape (*e.g.*, crosslinking density) [112]. The obtained release rate was constant (23 ng/day), as the mechanical properties maintained during the release period (over three weeks). The obtained release pattern was nearly zero-order with minimal burst effect and over 83% of released protein, in the first week, was bioactive [112]. Thus, this protein carrier can be useful for sustained, local delivery of cytokines; however, there are still a number of issues which may have an impact on the stability profile of loaded proteins that should be addressed. First, the remarkable drop in the bioactivity profile for vascular endothelial growth factor shown after the first week of release as a result of hydrolytic degradation and acidic degradation products ($pH < 5$) accumulated inside the elastomers. Second, the use of ultraviolet radiation during the photo-curing of this elastomer was reported to denature some of the loaded proteins and consequently destroys part of their biological activity [112]. Also, the use of organic solvents during the device preparation may change the protein conformational structure (denaturation), as reported previously [147].

In an attempt to avoid interior microenvironmental pH drop, Chapanian and Amsden evaluated the effect of decreasing the acidic nature of aforementioned PRP by replacing ε-caprolactone or ε-caprolactone & D,L-lactide with trimethylene carbonate [148]. The developed photo-cured elastomers revealed that the degradation and less acidic nature of carbonate group significantly improve the stability of loaded protein. They also showed the sequential delivery of bioactive vascular endothelial growth factor (VEGF165) and hepatocyte growth factor (HGF) by UV-crosslinking of a dual-layered cylinder, in which VEGF165 was in the outer layer and HGF in the inner layer [111]. A constant release of VEGF165 alone was first obtained, followed by overlapping and constant release of the two growth factors after a period of 4 days [111]. Nonetheless, the use of organic solvents and ultraviolet radiation during the photo-curing is still an issue that should be addressed, since it has an impact on the stability and bioactivity profile of loaded proteins. In that respect another attempt to avoid the harsh effect of UV-irradiation and organic solvents, visible light photo-crosslinking of acrylated poly(decane tricarballylate) was introduced by Shaker et al. They have formulated IL-2 loaded elastomeric matrices in the presence of CQ as a biocompatible PI and under solvent-free conditions [63]. The obtained results throughout a release period of 28 days, utilizing the same osmotic driven release mechanism, concluded that IL-2 was released in a controlled manner retaining of more than 94% of its initial activity [91]. The IL-2 release rate also increased by increasing the elastomeric device's surface area and decreasing the crosslinking density [91]. Therefore, the avoidance of UV-crosslinking drawbacks, the usage of solvent-free preparation process, the sustained delivery ability [92], and the proven biocompatibility [55] make these elastomers excellent candidates for use in thermosensitive therapeutic protein and peptide delivery.

From the aforementioned examples we can reveal that, the manufacture of photo-cured bioelastomers containing drugs, therapeutic proteins, bioactive molecules and cells is feasible. Whereas, it is still a great challenge to use visible light instead of harmful UV light in the preparation. As well, avoiding the organic solvents during the manufacture highly implements negative effects on the solvent-sensitive bioactive molecules and surrounding tissues during application. Meanwhile, the proceeding examples successfully resolve these highlighted challenges, nevertheless, to date there are no *in vivo* preclinical or clinical studies on the therapeutic efficacy of all of the aforementioned bioelastomeric carriers. More *in vivo* investigations and studies for the efficiency and biocompatibility are still required to examine the ability of these photo-formulated elastomers to fit clinically in the delivery of therapeutic proteins. Such examination and studies are also essential before seeing these photo-irradiated bioelastomers in the manufacture pipelines.

4.2. Hydrogels

Photo-irradiated hydrogels are a three-dimensional jelly like network composed of colloidal dispersion of PRP in aqueous medium, held together by crosslinking bonds (mostly covalent) [17]. Conducted researches proposed them as effective carriers for localized and controlled delivery of various drugs. Due to high water content they hold a good biocompatibility and consistency similar to a large extent to that of soft body tissues [25]. Having porous architecture upon swelling established them for a good permeability for macromolecules throughout their matrices as well as complete recovery within the release profile [77].

Two general strategies have been explored to formulate and load drugs into the photo-irradiated gel networks. The first one involves mixing the suitable PRP and PIS with the drug and then photo-irradiating it to entrap the drug within the matrix [77]. In this strategy, the drug stability and activity must be evaluated to ensure that it can withstand the photo-irradiation condition and will not react with any component in the system. In the second strategy, pre-irradiated hydrogels are incubated with the drug, in a suitable solution form till equilibrium for a sufficient time, to allow drug diffusion into the network during swelling [15]. On this basis, it is important to ensure that the photo-irradiation conditions are only sufficient for network formation without over crosslinking, because low molecular weight drug will not be able to diffuse through the extensively crosslinked network.

Although chemical crosslinking of hydrogels is reported to be the commonly used formulation methods [33,74], the photo-irradiation strategies have been reported to be more successful and effective when used for viable cells or macromolecule delivery [4,33,73,74,126]. This approach provides many advantages over chemical and physical crosslinking. First, reported photo-irradiated hydrogels are more often prepared at physiological pH and room temperature with minimal exposure to mild light source, which avoid the cross reaction and toxicities accompanying the use of chemical crosslinkers [5,149]. The mild formulation allows viable cells to be seeded homogeneously within the hydrogels in biologically compatible conditions [4,149]. Table 5 lists representative examples for viable cell delivery with some details.

Second, pharmaceutical carrier with predictable drug release rate can be conveniently achieved through photo-irradiated hydrogels. The released amount can be temporally controlled by changing the crosslinking density of the developed network, through altering PI concentration and light exposure time [15,150]. In such manner, the delivery of highly potent, but relatively toxic, anticancer drugs without inducing tremendous side effect was revealed [98,100,150,151]. These also include DNA delivery [73,125], controlled release of peptide and protein [147,152], and live vaccine delivery [122].

As a drug delivery example, photo-irradiated paclitaxel loaded hydrogels showed highly predictable drug release profiles that depended mainly on the network erosion rate and the formulated implant geometry [100,151]. Guo et al. synthesized paclitaxel loaded biodegradable hydrogels by the UV-irradiation of fumarate-based unsaturated poly(ester amide) and PEG diacrylate. Sustained release of paclitaxel was achieved over a two-month period without an initial burst release from this hydrogels [151]. Also, Missirlis et al. prepared doxorubicin encapsulated hydrogel nanoparticles by laser irradiation of acrylated pluronic F127 with PEG diacrylate, in which the drug was released in a sustained manner, with a minor burst effect, over a period of one week [98]. Table 2 lists more details regarding some of these controlled drug delivery examples.

As a therapeutic protein delivery example, Sun et al. developed angiogenic growth factors containing disc-shaped biodegradable hydrogels by UV-irradiation of dextran-allyl isocyanate-ethylamine and PEG diacrylate for use in therapeutic vascularization and wound healing [77]. The *in vitro* release studies showed that within the first 10 h, almost 35% of the encapsulated growth factor was released with a total of 50% released in the first 4 days. This predictable release profile revealed that these hydrogels might be able to mimic the normal physiological paracrine release pattern for VEGF. Five weeks following the subcutaneous implantation of these VEGF loaded hydrogels in experimental female Lewis rat model showed that great tissue in growth was achieved, implicating the bioactive role of VEGF in promoting vascularization. Tables 3 and 4 have more details of protein/peptide delivery examples.

Similarly, Chun et al. successfully developed pluronic hydrogels in which the pluronic F127 diacrylated and DNA plasmid were mixed together and photo-irradiated by UV light. The release of DNA from the obtained colloidal gel was sustained for more than three weeks and depends mainly on the crosslinking density (UV-irradiation time and presence of crosslinker *e.g.* acrylated hyaluronic acid). The sustained release profile and the transfection effectiveness of released DNA indicated that photo-crosslinked pluronic hydrogels are a promising platform for sustained delivery of therapeutic gene [73]. Table 5 shows more details regarding some of these gene carriers.

Third, photo-formulated hydrogels magnify the efficient pharmaceutical carriers in the targeted delivery through various strategies including: achieve stimuli responsive release pattern [153]; accomplish *in situ* photo-crosslinking to the specific delivery site of a targeted tissue [154]. For instance, Lee et al. investigated the thermogelling character for photo-irradiated pluronic hydrogels (*i.e.* a reversible sol–gel transition behavior at a certain temperature range) and its used as thermosensitive delivery system [153]. Site specific delivery was shown when Serra et al. irradiated modified poly(acrylic acid) with PEG by UV to develop novel acrylic-based hydrogels for use as a mucoadhesive delivery vehicles [154]. Furthermore, photo-irradiation prepares a multilayer hydrogels to combine various properties (such as pH sensitivity, high water absorption, and constant drug release), that might be required for a particular application [133,155]. For example, Lu and Anesth investigated the use of photo-irradiated multi-laminated poly(HEMA) to create layered matrix devices with non-uniform concentration profiles seeking pulsatile drug release realm [133].

As seen from the aforementioned, the applications of photo-irradiated hydrogels as delivery vehicles are tremendous and tailorable for different drugs. However, they still possess few circumscribing limitations and properties. First, those photo-formulation conditions are not suitable for cationic PIs because the presence of water inhibits their actions [52]; second, photo-cured hydrogels made from photo-irradiation of natural PRP like chitosan [77], inulin [77], and silk fibroin [77] are frequently immunogenic and are more difficult to manipulate or process than synthetic PRP; finally, hydrogels made from photo-irradiation of dextran [77] are typically characterized by weakness in their mechanical properties, batch-to-batch variations and control over the release rate were difficult to achieve. On the other hand, hydrogels made from photo-irradiation of synthetic PRP can be reproducibly and reliably manufactured (*i.e.*, provide a consistent source) and their sterilization is often easier. Chemical modifications can be easily made to tailor their properties and mechanical strengths to a specific

application. Nevertheless, they posses few limitations, for example, the achieved sustained release was always short and high percentage of release was achieved in the first few minutes or hours (burst effect) [77].

4.3. Micro/nano-particles

Photo-cured micro/nano-particles are brilliant pharmaceutical carriers, employed as either a drug-encapsulating vehicles or drug-embedded matrix to deliver the loaded drug in a controlled and/or sustained manner for definite periods, ranging from hours to weeks. Micro/nano-particles can easily be obtained by irradiating an aerosol, emulsion, or microemulsion composed of well-dispersed PRP-containing droplets. Such a quick formulation provides advantages over traditional methods of preparation. Mainly, photo-irradiation gives the sufficient stability to self-assembled micro/nano-sized particles against collapse during application. Keeping their well-defined configuration in space is crucial and specifically needed for the delivery of drug(s)/molecule(s) that should be secured or protected from the uncontrolled burst release during their *in vivo* circulation [114,156]. Photo-formulated particles not only slow down the release of the loaded drugs but also tailor the release rate and pattern through adjusting the applied electro-magnetic energy (intensity and period of implemented light) [66]. In addition to their high encapsulation efficiency for a variety of biomacromolecules, gene and viable cells [114,120], photo-irradiated micro/nano-particles are reported to be typically made from or incorporated inside a PRP like modified hydroxyethylstarch [76], polyglycidol [157], polyanhydride/gelatin [118], poly(lactic-co-glycolicacid) [30], poly(propylene fumarate) [43], $CaF_{(2)}$:$Ce^{(3+)}$/$Tb^{(3+)}$-poly(acrylic acid) [102], and PEG diacryalate/ GFLGK peptide diacrylate [123].

There are few research reports in which bioactive molecules or viable cells have been incorporated in photo-cured microparticles with a comprehensive study of their biomedical application. As such, Dai et al. combine the vacuum nano-casting technique with UV-irradiation to formulate CaF(2), Ce(3+)/Tb(3+)-poly(acrylic acid) as doxorubicin HCl loaded hollow microspheres. These hollow microspheres typically target the cancer cells through environment-dependent drug release pattern (pH variation) [102]. During their distribution within blood plasma (neutral pH) the release is too low, due to the electrostatic attraction between negatively charged photo-irradiated poly(acrylic acid) and positively charged doxorubicin, which switched off the release [102]. However, at the extracellular matrix and inside the endocytic vesicles the low pH neutralizes the photo-irradiated poly(acrylic acid) that quickly shifts to a fast release mode [102]. Such a smart pH-triggered drug-release property enables their use as promising pharmaceutical carriers for targeting anti-cancer drugs, however, no biodegradability evidence for these microspheres is revealed. The use of non-degradable microspheres requires a second surgical visit to the site of injection for the removal of the depleted microspheres. It is also important to mention here that photo-cured microspheres are limitedly used for the delivery of drugs/proteins that are either released to work in the extracellular space or have the self-capability for cellular internalization. In consequence with that, microspheres are non-relevant for the target of genes/drugs that are designed to function inside the cell or therapeutic proteins that work through direct actions with intracellular compartments.

Meanwhile, photo-formulated microspheres have been more potentially serving in the encapsulation and delivery of viable cells [114,129,130]. Using this approach, some researchers encapsulated viable cells for the secretion of either specific peptide/protein hormones or signaling molecules to activate other cells for treating diseases and remedy defects (Table 6). As such Cruise et al. encapsulated porcine islets of Langerhans inside laser cured PEG diacrylate microspheres to serve as an immune barrier for pancreatic cell transplantation [130]. Successfully, they revealed that photo-formulated microspheres were able to achieve greater than 90% encapsulation efficiency in adequate condition to keep more than 90% of islet viability. The high blood glucose levels will be able to diffuse from the blood vessels into the photo-formulated thin wall microcapsules to the encapsulated islet, allowing the responsive release of insulin to control the blood glucose level. [130], while some other researchers incorporated viable cells as tissue engineering implants with the main goal of targeting the release of these cells in the defect sites to reconstruct replacement tissues. For instance, Young et al. encapsulated murine fibroblasts in poly(vinyl alcohol) microspheres formulated through combining photo-irradiation with submerged electrospray technique [129]. Further, *in situ* UV-irradiation of RGD-grafted N-methacrylate glycol chitosan incorporated with adipose-derived stem cells and growth factor loaded microspheres was explored by Sukarto et al. [114]. Typically they photo-encapsulated stem cells with bone morphogenetic protein-6 (BMP-6) and transforming growth factor-β3 (TGF-β3) for promoting their chondrogenic differentiation, as a delivery strategy for cartilage tissue regeneration. Nevertheless the photo-crosslinked chitosan network merely has provided a successful vehicle for stem cell differentiation during chondrogenesis. At the same time the sustained co-delivery of those growth factors augmented the rate and extent of cartilage repair [114].

From the previous we can infer that using photo-irradiation keeps the integrity of microspheres, to guarantee that the isolation of whole cells from the immune system is precisely and accurately enough for transplantation surgery. Keep it in mind that the body exposure to a single uncovered cell might illicit the immune response to cause rejection of the photo-formulated cell carrier. At the same time photo-formulation provides the needed conditions for the cell to adhere, grow, propagate and differentiate through establishing the ultimate mechanical strength and high surface area to volume ratio. As well, maintaining the sufficient permeability to diffuse growth nutrients to the encapsulated cells and release signaling molecules to surroundings.

As nano-sized particles are the proper choice for intracellular delivery, many research studies investigated the adequacy and effectiveness of using photo-cured nanoparticles as pharmaceutical vehicles (Tables 2–5). Often the formulation occurs by simple mixing of drug(s) with PRP before nano-assemblage and photo-irradiation process [11], however, some researchers load the candidate drug(s) after preparing the particles and before integrating them through photo-irradiation. For example, the photo-irradiated hyaluronic acid nanoparticles loaded with paclitaxel were reported by Yoon et al. [158]. They have developed hyaluronic acid nanoparticles loaded with paclitaxel, using the simple dialysis method. The particles were then stabilized by UV-irradiation to formulate a tumor-targeting vehicle. The prepared particles demonstrated that photo-crosslinking sustained the release of paclitaxel in a linear manner for a prolonged period, without initial uncontrolled burst release, and maintained the stability of the formulated nano-assemblage in physiological conditions, as well. At the same time photo-irradiation did not affect the loading efficiency of the paclitaxel and the average size of the obtained nanoparticle [158]. Yoon et al. also reported that the *in vivo* antitumor activity of these nanoparticles was improved by photo-crosslinking, as a result of the increase in blood circulation time and stability inside the body [158]. Having said that this loading strategy is safe and a simple way for physical loading of small drug with high efficiency, nonetheless, those of biomacromolecule delivery, particularly proteins and genes, may find this method unsuitable.

In another strategy, some nanoparticles were prepared by the chemical conjugation of the drug within the PRP first followed by assembling into nanoparticles and photo-irradiation. For example, Dickerson et al. successfully conjugated doxorubicin with PEG-poly(aspartate-hydrazide-cinnamate) through acid sensitive hydrazone linkers. The conjugated PRP was then formulated as nanoparticles and UV-crosslinked [66]. The study demonstrated a competent controlled release behavior for the conjugated drug depending on the surrounding pH and degree of photo-crosslinking for PRP [66]. This chemical coupling strategy is optimal for maximizing the loading efficiency and sustaining the drug release, nonetheless, the conjugation condition might represent a harsh condition for keeping the chemical integrity of therapeutic proteins, particularly maintaining the stability of the tertiary structure proteins which is essential for the biological activity.

4.4. Micelles

Photo-formulated micelles have recently been expanded as one of the appropriate colloidal nanocarriers for the targeted delivery (Table 2) [37]. Although self assembled core-shell nanostructures have been widely used as carriers for various hydrophobic and amphiphilic drugs, photo-crosslinked micelles considerably offer a fast and stable formulation approach for drug encapsulation without affecting its physicochemical properties (Table 2) [159]. This *in vivo* stability was usually associated with prolonged plasma half-life and passive accumulation in the target tissues. A more recent study was conducted by Saito and his co-workers to demonstrate the feasibility of long term micellar aggregate stability of photo-crosslinked micelle synthesized by UV-irradiation of thymine-functionalized cores at short wavelength range [160]. Other promising photo-cured example is poly(ethylene oxide)-b-poly(glycidol-co-glycidyl cinnamate) micelles [159]. That carrier conjugated cinnamate with the glycidol to add a hydrophobic character to the backbone structure to facilitate their self assembly during micellization as well as UV sensitive double bonds to gain the photo-responsive ability [159]. Comparative ^{1}H NMR analysis for the photo-treated and untreated formulation illustrates that the kinetic stability of the obtained crosslinked carrier is predominantly due to photo-irradiation [159]. With the same photo-responsive moiety Kim et al. photo-irradiated PEG-b-poly(2-cinnamoyloxyethyl methacrylate)-b-poly(methyl methacrylate) micellar carrier [22]. They demonstrated in their study that UV-crosslinking is able to keep the micellar configuration in different external environments, even at different degrees of crosslinking [22].

From the previous examples it is very important to observe that, photo-irradiation is primarily responsible for the kinetic stability of the formulated micelles (crosslinking of PRP chains in the inner core), which is much more important than the thermodynamic stability (retaining the PRP at concentration above the critical micelle concentration). That kinetic stability is able to resist disassembly upon *in vivo* dilution and keeps the stable spherical core-shell structure for micelles without changing their biodegradability, to sustain the drug release at the target sites. Moreover, holding the micelle structure against dissociation upon dilution in various pH, might provide adequate protection to the loaded drug from the harsh environment of the gut. This characteristic feature allows the future use of photo-formulated micelles as a promising carrier for the various oral delivery perspectives.

4.5. Multifunction dendrimers

Photo-irradiated dendrimers have also been explored for preparing sustained-release delivery systems due to the postulated high surface area to volume ratio as well as their quantum size effect (Table 2). As highly branched, well-defined, and nano-size architected carriers, dendrimers can either encapsulate drug molecules into the interior of its branches before photo-irradiation process or chemically attach/physically adsorb drug onto the photo-crosslinked dendrimer surface [6,161,162]. Many of these incorporated drugs have been found to be consistently released through Fickian diffusion mechanism with an initial burst effect [6]. In a study conducted by Tasdelen et al. photo-cured poly(propylene imine) dendrimers were prepared in a photoreactor by the photo-crosslinking of poly(propylene imine) with methyl methacrylate [162]. However in a more convenient methodology for the synthesis, Zhang et al. photo-irradiated polyamidoamine-double bond and PEG-co-poly(glycolic acid)-co-methacryloylchloride to obtain a biodegradable dendrimeric drug carrier [6]. They also demonstrated its candidacy for Ofloxacin delivery and the potential of controlling the dendrimer structure in adapting the release rate [6]. Adversely, Grinstaff was able to photo-crosslink PEG-co-poly(glycerol-succinic acid) methacryl dendrimer *in situ* to successfully heal corneal wounds and injuries [161]. Simply he delivered the prepared biodendrimeric macromolecules as a liquid to the cornea and solidify it upon exposure to visible light as dendrimers crosslinked to a three-dimensional network [161]. With the success of his application *in vivo* in a chicken module, Grinstaff claimed that the prepared dendrimeric network can easily cure wounds associated with a LASIK procedure and secure a corneal transplant [161].

It is clear from these applications that photo-irradiation does a control over the dendrimers' architecture and size which potentially helps in reduction of toxicity and increase in trans-epithelial absorption. Moreover, photo-crosslinking improves the mechanical stability as well as keep the shape and uniformity for the assembled dendrimers. While this improvement in the nanostructure strength increases the drug encapsulation ability, the recognized architecture uniformity makes it promising platforms for both the drug conjugation and the viable cell delivery. The main rationale for this enhancement is that the photo-crosslinked dendrimer's void spaces are serving as drug delivery depots and useful to direct cell signaling and growth. Cells can be co-assembled with photo-crosslinked dendrimers and then place in hydrogels/bioelastomer to obtain three dimension implants with suitable macro-pores.

4.6. Nanofibers

Nanofiber producing technologies, such as electrospinning process, have long been combined with photo-irradiation techniques aiming to generate porous three-dimensional interconnected network structures with asymmetrical single or multiple reservoir features able to incorporate macro/micro molecular drugs (Table 2) [12,69,106,163]. Changing parameters such as the duration and intensity of irradiation, the chemical and elastic properties of PRP, and the injection speeds show that such nano-formulated carriers can be designed to be targeted, sustained, controlled, bioadhesive and/or stimuli-responsive delivery system. Meanwhile, photo-irradiated nanofibers offer an exciting opportunity to create biomimetic vehicle with precise architecture (shape and size) resembling native extracellular matrix elements in biological tissue, which are interesting for use in viable cell delivery. This kind of delivery was the focus of research conducted by Torres Vargas and his coworkers. This research group explored the electrospinning and photo-crosslinking of methacrylated PEG to prepare a bioactive nanofiber for wound dressing applications [106]. This photo-crosslinked nanofiber was able to quickly release the loaded *Calendula officinalis* extract as an anti inflammatory agent to promote the healing [106]. This study not only proved the ability of photo-crosslinked nanofibers to load macromolecular drugs, but also confirmed its higher ability to release the entrapped drug rapidly, due to their high swelling ability as well as their high porosity. Similarly, Liu et al. examined the possibility of preparing water insoluble nanofibers from polyvinyl alcohol grafted with styrylpyridinium group using also electrospinning combined with UV-crosslinking [69]. Their results demonstrated that UV irradiation was able to keep integrity, shape and mass of the prepared fiber during water immersion, as deemed characteristics for a good pharmaceutical carrier [69].

Furthermore, many other studies aimed at showing the advantages of generating another photo-created nanostructures included inside the photo-cured nanofibers to gather the dual functionality of two different nanostructures. For example Anka and her coworkers were able to *in situ* formulate gold nanoparticles and polyacrylonitrile nanofibers dually under UV-irradiation [12]. The imaging of the prepared fibers showed the resulted spherical nanoparticles that were uniformly scattered inside the collected nanofibers [12]. This study concluded that the photo-crosslinked nanofibers represent a dual vehicle; *i.e.*, one pharmaceutical carrier with two simultaneous actions, effects, and/or stimuli responses.

Photo-crosslinking of nanofibers increases their stiffness and rigidity that help in keeping their mechanical integrity especially during *in vivo* application. Meanwhile, photo-crosslinking increases the encapsulation efficiency as well as alleviates the initial burst release of the loaded active ingredient. However, to date, the vast majority of the studies on

electrospun photo-irradiated fibers were conducted *in vitro*. In depth and systemic *in vivo* studies are still deemed necessary before clinical translation or commercialization can be realized including the examination of *in vivo* drug release kinetics and dynamics, effects of photo-irradiation dosage and release kinetics on therapy efficacy, and biocompatibility of the photocrosslinked nanofibers.

4.7. Biomembranes

Photo-cured biomembranes have also been used as smart carriers for controlled delivery of various drugs with different molecular weights and solubility characteristics (Table 2). As such there are many research reports in which photo-irradiation has been utilized, either in the membrane preparation or in the drug incorporation, and demonstrated their feasibilities for sustained delivery [107,108,115,116,164]. For example, a Japanese research group (Kaetsu and his co-workers) used UV-irradiation for the synthesis and coating of their biofilm [108,110,164]. Easily, they developed methylene blue (MB) loaded biofilm by UV curing of casted hydroxyethyl methacrylate and MB mixture followed by coating through UV-irradiation of acrylic acid, tetraethyleneglycol dimethacrylate (crosslinker) and PRP mixture [164]. The obtained coat was pH responsive and showed MB permeation/diffusion that increased predominantly in the acidic environment. However they also showed that adding N-isopropyl acrylamide in the coating layer was able to adjoin a temperature responsive character to the controlled release of MB [108]. They also demonstrated the intelligence for substrate-responsive MB release ability of that membrane through the incorporation of glucose oxidase enzyme in the coating layer, which can elicit acidic environment in the presence of glucose as a substrate (by oxidation to gluconic acid) [164]. Moreover, they utilized this glucose-responsive photo-cured network to formulate a nicotine replacement device for smoking cessation [110]. The rate of controlled release for nicotine from that intelligent biomembrane was attributed mainly to hydrophilic/ hydrophobic property of the used photo-crosslinker [110].

Extendedly in the same scenario Ng et al. utilized the photo-curing for the preparation of poly(2-hydroxyethyl methacrylate) biomembrane coated with poly(acrylic acid) as another pH responsive delivery device [107]. At that instance, they compare the release profile for six miscellaneous drugs with differences in molecular weights (up to 570 Da), acid/base dissociation constants and solubility profiles. They revealed that the release was significantly correlated to the drug's Mwt (negative relation between the drug's Mwt and release rate) and pH controlled release was not observed in high Mwt drugs as that with low Mwt [107]. In another study conducted by them poly(2-hydroxyethyl methacrylate) membranes were prepared and coated with poly(acrylic acid) using the same formulation technique [109]. Through this study they investigated the effect of drug's Mwt and charge on the release behaviors with the use of cationic (MB), anionic (metanil yellow), and neutral (caffeine) drugs. Their results revealed that drug release through those membranes depended to a large extent on the electrostatic interaction between the encapsulated drug and the predominant functional group within the photocrosslinked layer [109].

Another promising perspective for the photo-irradiated biomembranes was illustrated by Plewa et al. when they showed viable cells (human bone marrow stromal) delivery for UV-irradiated multilayer biomembrane [132], along with Lee et al. where they showed the anti adhesion properties for photo-crosslinked gellan gum cinnamate membrane [165] and with Peppas et al. where they revealed the remarkable response of photo-irradiated biomembranes to specific internal biomolecules, such as glucose or cholesterol [166,167]. Successfully, Peppas and his co-workers explored the use of such biomimetic membranes as robust micro/nanosensor network for various sensor platforms (such as micro/nanocantilevers) [166,167]. In particular, the physicochemical recognition of cholesterol was shown through a biomimetic network composed through photo-irradiation of methacrylic acid and PEG dimethacrylate in tetrahydrofuran and dimethyl sulfoxide [167]. It was also of interest as they note that, the porosity of that photo-irradiated network significantly increased their bio-recognitive properties and decrease the recognition time [167]. Similarly, another biomimetic network composed through photo-irradiation of PEG dimethacrylate and acrylamide showed recognition properties for glucose moiety [166].

5. Conclusion and future perspective

Research underlying photo-irradiation paradigm has certainly spanned in the last decades to precisely prepare a wide range of pharmaceutical carriers mimicking biological systems. The intelligence of photo-irradiation in tailoring the pharmaceutical carrier's architecture to a specific use, elaborates its ability to produce delivery systems suitable for micro/macro-molecules. As well, the holistic diversity in the afforded PRP expands the accessibility of getting targeting carriers with specifically triggered properties. Despite the fact that these prosperous carriers target and sustain the delivery of loaded molecules, the photo-formulation technique is still in its early stage of development and no products are yet available in the market. Clinical approval for those delivery vehicles has yet to be investigated.

In order for this technique to be clinically adopted, two requirements must be fully satisfied: adaptability and biocompatibility. To this end, connecting the scientific background of photo-irradiation with clinical requirements helps generate the adaptable and favorable formulating conditions. Also further understanding for peripheral/undesired effects associated with photo-irradiation that might have a significant bio-incompatibility potential, together with the increase in collaboration of scientists from different disciplines, will persuade investigators to smarter and friendlier formulation conditions to intimate the effective delivery of biologics. Deep studies on the interactions between *in vivo* biological systems and photo-irradiation will play a significant role in the future developments of the formulated carriers. Another highlighted area of future investigation is expanding the application of *in vivo* photo-formulation for delivering the bioactive molecules/cells, to avoid the invasive surgery during implantation and improving the patient compliance. The PRP can be simply incorporated with PIS to be injected inside the body using needles, catheters, and laparoscopy and the light can be simply applied transdermally or through these injectors. Expanding this concept has a significant market potential and implements unimaginable biomedical applications.

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