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Curcumin-loaded Alginate Hydrogels for Cancer Therapy and Wound Healing Applications: A Review

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Abstract

Hydrogels have emerged as a versatile platform for a numerous biomedical application due to their ability to absorb a huge quantity of biofluids. In order to design hydrogels, natural polymers are an attractive option owing to their biocompatibility and biodegradability. Due to abundance in occurrence, cost effectiveness, and facile crosslinking approaches, alginate has been extensively investigated to fabricate hydrogel matrix. Management of cancer and chronic wounds have always been a challenge for pharmaceutical and healthcare sector. In both cases, curcumin have been shown significant improvement and effectiveness. However, the innate restraints like poor bioavailability, hydrophobicity, and rapid systemic clearance associated with curcumin have restricted its clinical translations. The current review explores the cascade of research around curcumin encapsulated alginate hydrogel matrix for wound healing and cancer therapy. The focus of the review is to emphasize the mechanistic effects of curcumin with its fate inside the cells. Further, the review discusses different approaches to designed curcumin loaded alginate hydrogels along with the parameters that regulates their release behavior. Finally, the review is concluded with emphasize on some key aspect on increasing the efficacy of these hydrogels along with novel strategies to further develop curcumin loaded alginate hydrogel matrix with multifacet applications.

Keywords: Curcumin; alginate; hydrogel; cancer; wound-healing

1. Introduction

The research theme of designing innovative delivery vehicles concerning the carriage of pharmaceutically significant biomolecules/drugs has been the center of attraction globally. In this regard, polysaccharides have been an eminent contender due to their ability to render materials with controlled properties and to act in a synergistical fashion with different materials [1]. Polysaccharides are an established class of fascinating materials used in a wide range of biomedical applications owing to their biocompatibility, biodegradability, enhanced bioavailability, and abundance in occurrence [2]. The presence of hydrophilic groups (hydroxyl, amine, carboxylic) in the structural architect of polysaccharides renders them the ability to support cell growth and proliferations which is an important aspect for clinical interventions [3]. The presence of these functional groups endows polysaccharides with additional incredible properties for instance antibacterial, antioxidant, anticoagulant, antimycotic, and wound healing [4-6]. Among other polysaccharides, alginate has been extensively explored due to its exquisit suitability for biomedical applications specially in wound healing, tissue engineering and cancer therapy [7, 8].

For a system to be apposite for wound healing applications it should be able to fill wound spaces, should be able to provide antibacterial properties should be able to address mechanical stability and good penetrability to metabolites and water vapor [9]. For an effective intervention and repair of a wound, which is a complex process, the site of wound is protected from invading pathogens [10, 11]. The process of wound healing comprises of series of events that includes three biological stages: inflammatory, proliferative, and tissue remodeling. An efficient would healing approach should be proven effective in regulating all the three phases effectively and efficiently [12].

These requirements are analogous in case of cancer treatment as well where the transportation and localization of chemotherapeutic drug to the target site is a vital aspect in the treatment process [13]. The ill effects of chemotherapeutic drugs, water insolubility, less bioavailability, and non-selective actions of treatment procedures poses serious consequences while conceding patient's recovery and welfare [14]. Hence, to address these impediments, encapsulation of chemotherapeutic drugs has been accepted as a promising approach [15, 16].

Constant efforts are underway to design efficient delivery platforms of which, hydrogels have gained substantial interest of being a persuasive approach for delivering therapeutics/biomolecules across the target site [17]. Hydrogels are composed of natural or synthetic macromolecules crosslinked to form a three-dimensional network with an ability to absorb huge amount of water and share a close similitude to biological tissues [18]. Hydrogels supports cell attachment and proliferation due to their structural architect that allows the exchange of gases, bioactive molecules across their networks along with elimination of harmful materials [19]. Encapsulation of drugs in the hydrogel network and their localization at the target site has been increasingly explored for their utility in biomedical applications.

As a potent drug, curcumin ((1E, 6E)-1, 7-bis (4-hydroxy-3-methoxyphenyl)-1, 6-heptadiene-3, 5-dione), a polyphenolic compound extracted from *Curcumalonga* has been shown to have significant benefits for the human body [20] specially in cancer treatment [21] and wound management [22]. Curcumin is demonstrated to target multiple signaling molecules while have also been reported to show activity at the cellular level supporting its health benefits [23]. While a lot of therapeutic interventions appear to be associated with curcumin, majority of the advantages are as a result of its antioxidant and anti-inflammatory features [24].

Despite its benefits, Curcumin has limited applications in the clinic due to its hydrophobic nature and subsequent low solubility in aqueous environment, and poor bioavailability [25, 26]. This minimal bioavailability is often as a result of poor absorption, rapid metabolism, and rapid elimination [27]. Developing alginate-based hydrogels has been a key approach to address the poor aqueous solubility of curcumin. Alginate being a hydrophilic biopolymer offers substantial features that includes biocompatibility, biodegradability, non-toxicity and biostability that are highly desirous for various biomedical and healthcare applications [28]. The application of alginate-based hydrogels loaded with drugs, growth factors and other bioactive molecules has gained considerable interest from many research groups for their utility in drug delivery and wound healing applications owing to their designing flexibility, versatility in terms of functionalization, tunable intrinsic properties, multifacet responsiveness towards external stimulus [29, 30].

The current review provides a brief overview of the cascade of research around curcumin encapsulated alginate hydrogels for wound healing and cancer therapy. The focus of the review is to emphasize the biological effects of curcumin with its fate inside the cells upon ingestion. Further, the review provides different approaches to encapsulate curcumin in the alginate hydrogel network along with the parameters that govern their release behavior. Finally, the review is concluded with emphasize on some key aspect on increasing the efficacy of these hydrogels along with novel strategies to further develop alginate-based hydrogels with multifacet applications.

2. Curcumin

2.1 Mechanism of action of curcumin

2.1.1 Cancer Biology

Curcumin is a highly diverse molecule with pleiotropic mechanism of action which targets multiple molecules involved in cancer initiation, development, and metastasis [31]. It targets key enzymatic reactions in the molecular pathways thereby inhibiting the activity of many growth factor receptors and cofactors, modulating the expression of inflammatory cytokines which may lead to cancer metastasis, inhibit the proliferative proteins, and cell cycle protein to arrest cancer cell proliferation and activates apoptotic proteins to eliminate cancer cells [32].

2.1.2 Wound healing

Wound healing is a cascade of highly regulated steps which involves Inflammatory phase, granulation phase followed by the reconstruction phase and collagen deposition [33]. Curcumin has the potential to targets each of these phases by inhibiting pro-inflammatory cytokines to alleviate inflammation, scavenging reactive oxygen species, activating specific growth factors to initiate granulation and fibroblast differentiation to induce collagen deposition and wound reconstruction [22]

2.2 Molecular targets of curcumin

Curcumin being a highly pleiotropic biomolecule, directly and indirectly targets multiple molecules and modulate their activity and functions. More than 20 different types of molecules have been found to directly interact with curcumin, including transcription factors, enzymes involved in DNA synthesis; DNA polymerases [34], Adhesion molecules; focal adhesion kinase (FAK) [35], enzyme involved in ROS production, thioredoxin reductase [36], Signalling molecules, protein kinase (PK)-C [37], lipoxygenase (LOX) [38], and tubulin [39] and several proteins involved in apoptosis and proliferation. Additionally, curcumin has shown effective binding with heavy metals and divalent metal ions including Fe, Cu, Mn and

Zn which works as cofactors in several molecular reactions [40, 41].

2.2.1 Targeting enzymatic reactions to restrict cancer growth and metastasis

Curcumin modulates a variety of enzymes that are closely associated with inflammation and cancer. These enzymes include Lipoxygenases (LOXs) [42, 43], Cyclooxygenase (COX-2) [44, 45], Inosine monophosphate dehydrogenase (IMPDH) [46, 47], and aminopeptidase [48]. A substantial number of studies have shown that COX-2 is overexpressed in a wide variety of human cancers and IMPDH is a rate-limiting enzyme that converts inosine monophosphate to xanthosine monophosphate [49]; its enhanced expression is correlated with increased cellular proliferation and malignant transformation. Curcumin can downregulate the expression and the activity of COX-2 [50, 51] and IMPDH thereby aid in restricting the growth of cancer cells [52]. On the other hand, LOXs enzyme catalyse the formation of hydroperoxides from linoleic acid and arachidonic acid and are highly expressed in immune and tumor cells that involved in inflammation, and tumorigenesis [53]. Curcumin directly binds to lipoxygenase and inhibits their activity [42]. Further, *aminopeptidases* enzyme catalyses the cleavage of peptide bonds which result in release of amino acids from the amino terminus (N-terminus) of proteins or peptides (exopeptidases) [54].

As cancer cells are highly dependent on the exogenous supply of amino acids for their survival, overexpression of aminopeptidase is highly prevalent in variety of tumors [55]. Curcumin irreversibly binds with aminopeptidase and inhibits tumor invasion and angiogenesis of different human cancers [48]. Curcumin has also been shown to inhibit xanthine oxidase activity, an enzyme of purine metabolism that generates reactive oxygen species (ROS) [56]. Curcumin has also demonstrated that it can inhibit phosphatidylinositol-3 kinase and induce autophagy in malignant tumor cells [57]. Other important enzymes that are

downregulated by curcumin include arylamine-N-acetyltransferase [58], ATPase [59], desaturase [60], farnesylprotein transferase (FPTase) [61], iNOS [62] MMP [63, 64], NAD(P)H dehydrogenase quinine [65], ornithine decarboxylase (ODC) [66], and telomerase [67]. Directly or indirectly these enzymes are involved in the cancer proliferation and metastasis which gets checked upon curcumin administration.

2.2.2 Targeting multiple molecular pathways

Curcumin can inhibit many molecular pathways that contribute to its anti-inflammatory and anti-carcinogenic effects.

2.2.2.1 PI3K-AKT signal pathway

phosphatidylinositol-3-kinase (PI3K) / protein kinase B (AKT) pathway is an intracellular signal pathway that promotes proliferation, cell survival, growth, angiogenesis in response to extracellular signals. It is commonly dysregulated in lymphoma and closely associated with the tumorigenesis and resistance to radiotherapy [68]. Curcumin downregulates this signalling pathway by modifying the expression of key genes, proteins, and miRNA [69, 70]. Akt, is a member of the family of phosphatidylinositol 3-OH-kinase regulated Ser/Thr kinases, curcumin phosphorylates Akt by an increased phosphorylation of glycogen synthase kinase 3beta (GSK3beta) [71] Studies show that miRNA-203,206 and miRNA-192-5p can inhibit tumor proliferation, invasion, migration, EMT, in variety of cancer cells [72, 73]. Curcumin inhibits cell proliferation and induce apoptosis in non-small cell lung cancer (NSCLC) cells via up-regulating the expression of miRNA-206/miRNA-192-5p resulting in inhibition of PI3K/AKT/mTOR signalling pathway [74, 75].

2.2.2.2 JAK-STAT signal pathway

The Janus kinase/signal transducer and activator of transcription (JAK/STAT) signalling pathway is a centre for many vital cellular processes, its dysregulation is associated with various cancers and inflammatory conditions [76]. Several studies have shown that the modulation of JAK/STAT pathway by curcumin is involved in reduced migration and invasion of cancer cells [77]. Curcumin modulates this pathway by targeting multiple miRNAs; downregulation of miR-99a in human cancers, indicating the potential role of miR-99a as a tumor suppressor. Curcumin inhibit JAK/STAT signalling pathway by upregulation of miR-99a [78].

2.2.3 Targeting proliferative and apoptotic proteins

Curcumin target cell cycle regulatory proteins to control the proliferation and cell division in cancer cells, it suppresses the cancer cell proliferation by down-regulating cyclinD1 and up-regulations of p21 expression [79, 80]. Curcumin could reduce the anti-apoptotic protein Bcl-2 and enhance the expression of pro-apoptotic protein Bax which result in cleavage of caspase proteins, and apoptosis [81, 82].

2.2.3.1 Wnt/β-catenin signal pathway

WNT/β-CATENIN signalling pathway is evolutionarily conserved pathway that plays a prominent role in maintaining cellular homeostasis [83]. Activation of wnt/ β-catenin pathways can modulate cell proliferation, apoptosis, differentiation, migration, invasion, cell renewal. Beta-catenin is the core component and essential for the activation of wnt/ β-catenin signalling [84]. In osteosarcoma, curcumin reduce the expression of miR-21, and inhibit expression of Beta-catenin and GSK-3b protein to inhibit this signalling pathway [85]. In NSCLC, curcumin enhanced the expression level of miR−192−5p and decreased the expression of c−Myc leading to the inactivation of wnt/ β-catenin signalling pathway [86]. In

case of colon cancer treatment, curcumin down-regulate miR-130a, to inhibit wnt/ β-catenin pathway [87].

2.2.3.2 MAPK signal pathway

The mitogen-activated protein kinase (MAPK) cascade is a key signalling pathway that regulates various cellular processes under normal and pathological conditions [88, 89]. Curcumin can inhibit proliferation and migration of human glioblastoma cells by upregulating the miR-378 miRNA, which is considered a tumor suppressor miRNA, to inhibit tumor cell proliferation, invasion and migration in glioblastoma [90, 91]. Yu *et al.* showed that curcumin reduces the retinoblastoma cell viability and induced the apoptosis of Y79 cells through the activation of JNK and p38 MAPK pathways [92]. Curcumin inhibits the growth and invasion of human monocytic leukemia SHI-1 cells *in vivo* by regulating MAPK and MMP signal transduction [93].

2.2.3.3 P53 signal pathway

TP53 also described as the 'guardian of the genome' codes for a protein called tumor protein p53 [94]. This protein acts as a tumor suppressor and regulates uncontrolled cell division by controlling DNA repair, apoptosis, and cell cycle arrest [95]. TP53 is the frequently mutated gene in most of human cancers [96, 97]. In breast cancer, mutated p53 is associated with lower survival rates and resistance to conventional therapies [98]. Curcumin target breast cancer cells by up-regulating the expression of p53 and Bax and down-regulating the antiapoptotic proteins MDM2 and Bcl-2 [99].

2.2.3.4 NF-κB signal pathway

NF-kB is a transcription factor involved in a wide variety of biological activity. It works as a

master regulator which mediates a crosstalk between inflammation and cancer at several steps. Aberrant expression of NF-kB is highly associated with the human malignancies [100, 101] and suppression of this pathway has turned out to be a potential therapeutic approach for cancer treatment. Studies showed that curcumin impair NF-kB pathways to inhibit invasion and proliferation of cervical cancer cells [102] and restrains stemness features in liver cancer [103]. Under hypoxic conditions, curcumin interfere with tumor-stromal crosstalk via ERK/NF−kB axis to attenuate the malignancy of pancreatic cancer cell [104].

2.2.3.5 Histone deacetylases (HDACs)

Histone deacetylation is a major histone modification which are considered important epigenetic changes to alter the expression of genes. Their dysregulation can lead to the risk of cancer [105]. HDACs eliminate the acetyl group from histone proteins which are associated with gene silencing. Curcumin is the most potent inhibitor of HDACs [106]. It has been shown that curcumin induce global inhibition of HDAC activity and reduce HDAC8 isoform activity in the leukemic cell [107]. Inhibition of HDACs, lead to increased levels of acetylation, curcumin inhibited high levels of HDAC1, 3 and 8 in the Raji cells which resulted in increased acetylation levels of histone H4 [108] and directly inhibited HDAC4 transcription in medulloblastoma cells [109].

2.2.4 Histone acetyltransferases

Like the histone deacetylation, histone acetylation is a critical phenomenon in gene expression and regulation. Histone acetyltransferases (HATs) cause histone acetylation which lead to gene transcription. The balance between acetylation and deacetylation is important for the regulation of gene function. Irregular activities of HATs have been associated with the onset of cancer. Curcumin has shown inhibition of certain isoforms of HAT and considered

as a selective HAT inhibitor [110]. Curcumin specifically inhibit HAT activity of p300/CBP family [111, 112] by its Michael reaction acceptor function, enhances p300 degradation and inhibits histone hyperacetylation, suppress GCN5 linked with hypo-acetylation of histone H3, and p65 isoform of NF-kB [113].

2.2.5 DNA methyltransferase

DNA methylation has a vital role in regulating normal biological activities in living systems [114]. Methylation of DNA is a type of transmissible change in the DNA that can directly suppress the expression of a gene [115]. Both hypomethylation and hyper-methylation of DNA have been observed within cancer cells. Curcumin targets global genome methylation by targeting DNA methyltransferases. Studies have shown that curcumin covalently obstructs the catalytic thiolate domain C1226 of DNA methyltransferase I, Suppress methyltransferase M.SssI [116]. Which result in hypo-methylation of genome, WIF-I promoter, NrF2 promoter [117, 118].

2.3 Fate of curcumin inside the cells

2.3.1 Oral administration

The metabolism of orally ingested curcumin starts in the intestinal mucosa. Curcumin molecules first pass through a complex layer of mucus composed of glycoproteins and lipids to enter the systemic circulation. The mucus barrier results in the development of concentration gradient and biotransformation causing impairment in transmucosal passage of curcumin. Additionally, enterocytes, perform apical efflux of curcumin into the lumen [119, 120] resulting in further decrease in the bioavailability of curcumin in the blood plasma. The curcumin molecules uptake by enterocytes subsequently undergo metabolism through modification and conjugation [121] by several cytosolic and microsomal enzymes, like

oxidoreductases, sulfotransferases (SULTs), glucuronosyltransferases (GSTs), uridine diphosphate-glucuronosyltransferases (UGTs) and aldo-keto reductases. Several studies suggest that curcumin mostly undergoes reduction than conjugation by the sulfotransferases and glucuronosyltransferases.

Sulfation of native curcumin occurs to a minimal extent in enterocytes however reduced curcumin species, predominantly hexa- and octahydrocurcumin, constitute the preferred sulfotransferases substrates [122]. Epithelial cells in the lumen of the gastrointestinal tract contain several UGT isozymes, including UGT1A1 and UGT1A7 through UGT1A10 [123], of these, UGT1A7, 1A8, and 1A10 are predominantly expressed in the gastrointestinal tract than liver [124, 125], the organ most responsible for glucuronidation [126]. Furthermore, studies have shown that reduced curcumin including hexahydrocurcumin [127] and octahydrocurcumin extensively undergo glucuronidation in enterocytes than with nonreduced curcumin [122]. Another process contributing towards the low systemic bioavailability of curcumin is it getting associated with the intestinal non-detoxification proteins. In some instances, the binding of curcumin to a protein induces an inhibitory effect, as shown for several ATP-binding cassette (ABC) transporters [128] and CYP isozymes [129] or it can be both antagonistic and bio-transformative, as for SULTs [130, 131] and GSTs [132].

The reduction and subsequent conjugation of curcumin render this molecule more hydrophilic and facilitate their renal or enteral excretion. The enteral excretion either proceed directly from the intestinal mucosa back into the gut or indirectly via the circulatory biliary route. Transmembrane passage of the anionic moieties requires facilitated transport; cells possess transmembrane proteins that effectively traffic the biotransformed compounds across the hydrophobic barrier. ABC superfamily P-glycoprotein [P-gp/multidrug resistance protein

(MRP) 1 (MDR1)/ABC subfamily B member 1 (ABCB1)], present on the apical side of cells in the jejunum, colon, liver, and kidney [133] facilitate the transmembrane process of conjugated curcumin. The non-conjugated curcumin or other derivatives of curcumin that have been retained in the intestinal lumen or in enterocytes, are finally excreted as body waste, however, basolaterally transported curcumin and its metabolites could potentially target the tumor tissue but are also subject to the subsequent hepatic clearance (second pass effect) and uptake by nonenterohepatic organs.

2.3.2 Systemic administration

Systemically administered curcumin rapidly and effectively passes through the liver and subjected to hepatic clearance and biliary excretion. Holder *et al.* showed that majority of the intravenously administered curcumin (70% - 85%) was present in bile 2 and 6 hours after administration [134], however it was easily detectable in the bile within 30 minutes after administration [135]. Hepatocytes contain high concentrations of most phase I and II enzymes compared with other organs, which lead to the biotransformation of curcumin through reduction and conjugation [136]. The curcumin metabolites that have been basolaterally exported from enterocytes, hepatocytes, or nonenterohepatic organ cells are most likely to undergo renal clearance, given that the kidneys are responsible for the elimination of a myriad of conjugated compounds [137].

3. Different methods for encapsulating curcumin in the hydrogel netwrok

Curcumin is practically insoluble in aqueous medium due to its high log P value; it shows higher solubility in polar aprotic and polar protic solvents. To increase the water solubility of curcumin, surfactants, including amphiphilic (co)polymers, have been used after physically blending with curcumin [138]. However, the resulting curcumin–surfactant micelles or

vesicles are unstable, leading to rapid drug loss and failure during administration [139]. On the other hand, curcumin-polymer conjugates have also been prepared by covalently linking curcumin with water soluble polymers. Hydrogels are soft materials formed by physical or chemical cross-linking, which results in a three-dimensional network and are capable of trapping large quantities of water [140]. Curcumin based hydrogels were prepared through several chemical approaches including covalent interactions, electrostatic interaction and simple diffusion or partitioning.

3.1 Covalent interaction with hydrogels

Hydrogels prepared under covalent interaction are considered as chemical gels. In this process, the polymer is mixed with a gel initiator, a cross-linker, and a drug; then the system is allowed to polymerize in which a matrix loaded with the drug. Pan *et al.* prepared a multi-responsive self-healing curcumin-phenylboronic acid (PBA) hydrogel for the controlled release of curcumin was prepared using the Hantzsch reaction [141]. Curcumin was covalently conjugated to the PBA containing polymer by introducing a dynamic linkage between the 1,3-diketone group of curcumin and PBA moieties in the polymer chains. The conjugate was mixed with poly vinyl alcohol to yield a self-healing curcumin-loaded hydrogel based on the formation of dynamic boronic esters. The synthesized hydrogels had self-healing properties due to the dynamic nature of the borate linkages and the rate of curcumin release could be modified using multiple stimuli, resulting in shifting of the equilibrium between borate and boronic acid.

Curcumin is highly sensitive to oxidation; therefore Shpaisman, *et al.* developed a one-step synthesis method through condensation polymerization of curcumin, PEG, and DTE in the presence of triphosgene and pyridine as the catalyst to incorporate curcumin into the hydrogel

backbone and cross-linked through biodegradable carbonate linkages [142]. This curcumin polymeric backbone helps to protect the curcumin from oxidation and degradation, while hydrolysis of hydrogel result in the release of active curcumin. Nontoxic poly (ethylene glycol) and desaminotyrosyl-tyrosine ethyl ester were used to tune the hydrophilicity and hydrophobicity of the hydrogel.

Further, Chen *et al.* developed glycyrrhetinic acid (GA) modified curcumin supramolecular pro-gelator (GA-Cur) and Nap-Cur by replacing GA with the naphthylacetic acid (Nap) [143]. These progelator compounds showed high water solubility and could form glutathione (GSH) triggered supramolecular gels by disulfide bond reduction. These gels showed sustain release of curcumin and could be used for the treatment of liver cancer due to the over expression of GA receptor in liver cancer cells.

Covalent interactions are strong in nature and it helps in restricting the diffusion of drug loosely adsorbed on the surface of hydrogels. This in turn increases the loading as well as encapsulation efficiency of curcumin inside the hydrogel.

3.2 Electrostatic interaction

Electrostatic interaction between certain charged moieties can create reversible in situ-forming hydrogels. The electrostatic moieties can be easily prepared as an aqueous solution and remain in solution under physiological conditions without materials of different ionic species. The mixing of two different ionic hydrogel components can easily induce the formation of hydrogel via reversible electrostatic interaction between oppositely charged ionic materials under physiological conditions.

In this context, Yang *et al.* fabricated a curcumin loaded hydrogel by electrostatic interaction

using Mesona chinensis polysaccharide (MCP)-chitosan (CH) polyelectrolyte composite. Chitosan concentration could tune the elasticity, hardness, water-holding capacity, and thermostability of MCP-CH hydrogels; highest concentration of CA result in pronounced honeycomb structure. These gels showed good encapsulation efficiency of curcumin which can be further enhanced by increasing the concentration of CH. MCP-CH hydrogels provided prolong curcumin release, therefore, MCP-CH hydrogels have great potential as effective hydrophobic bioactive substance delivery vehicles in the delivery system [144]. Further, Teong *et al.* developed curcumin-loaded hydrogel nanoparticle derived aggregates through electrostatic field system using curcumin, biopolymeric chitosan, gelatin, and hyaluronan nanoparticles [145]. The prepared biopolymeric hydrogel nanoparticles show a narrow distribution with a small size of approximately 3-4 nm in diameter; these aggregates increased their size to approximately 26-55 nm after curcumin incorporation with a very high incorporation efficiency of 81, 67, and 73 % curcumin into the chitosan, gelatin, and hyaluronan nanoparticles respectively. The electrostatic interaction between the polymer and curcumin provided high stability to the drug.

3.3 Simple diffusion/partitioning

Hydrophobic drugs like curcumin are insoluble in water and are usually entrapped in hydrogels through simple diffusion or partitioning. These gels are more considered as physical gels and provide a sustained environment for drug release at stimulus. Gong et al, developed a biodegradable in situ gel composed of curcumin loaded micelles and thermosensitive hydrogel for cutaneous wound repair. Curcumin being highly hydrophobic was encapsulated in polymeric micelles (Cur-M), the hydrogel (Cur-M-H) was prepared by a one-step solid dispersion method using curcumin, poly (ethylene glycol)–poly(ε-caprolactone) (PEG–PCL) copolymer. Cur-M-H showed tissue adhesiveness and could release curcumin in

an extended period [146]. In this regard, Hamid *et al.* fabricated pH sensitive micelle-crosslinked 5-FU and curcumin hydrogel through a reversible Schiff's based reaction between gelatin-hydrazide (Gel-ADH) and self-assembled Pluronic F127-benzaldehyde (PF127-CHO) micelles. Curcumin was incorporated in core of micelles embedded in hydrogel and showed pH-responsive sustained release pattern of 5-FU in combination with curcumin [147]. Further, Ibilola *et al.* formulated curcumin-loaded liposomes formulations in lysine–collagen hydrogel for enhancing surgical wound healing. The hydrogel base was prepared separately, and then curcumin-loaded liposomes were infused to give hydrogel formulation [148]. In order to prepare hydrogel using simple partitioning process, Song *et al.* developed curcumin-enveloped methoxy poly(ethylene glycol)–poly(δ-valerolactone)–poly(ε-caprolactone) (MPEG–PVL–PCL) micelles embedded into Carbopol 940 hydrogel for full thickness dermal wound therapy [149]. In summary, the curcumin-loaded MPEG–PVL–PCL micelles-embedded Carbopol 940 hydrogel was demonstrated to be a potential candidate for the treatment of skin inflammation and full thickness wound healing.

The encapsulation /loading of curcumin inside the hydrogel network is regulated by many factors including the degree of crosslinking, concentration of crosslinker and polymer used, the level of interaction between the curcumin molecules and the polymers. Also, regulation of the reaction conditions (choice of solvent, method of removal of unbounded drug, sink conditions) and extrinsic factors like pH and temperature could be crucial in attaining the encapsulation of curcumin inside the hydrogel mesh.

4. Parameters affecting the release of curcumin from hydrogels

The generic structure of curcuminoids derived from the rhizome of the *Curcuma longa* (turmeric) is shown in **Figure 1a** comprises of curcumin, demethoxycurcumin, bis-

demethoxycurcumin, and cyclocurcumin. Out of all these biologically active curcuminoids present in turmeric, curcumin is the most abundant with a molar mass of 368.38 g/mol [150]. Reports from the clinical trials suggests that the human body has a high tolerance limit for curcumin at 8 g/day (no toxicity), and at 12 g/day (minimal toxicity) [151, 152]. Curcumin takes part in diverse biochemical pathways via H bonding (donor /acceptor), cation binding and Michael addition reaction due to the occurrence of many reactive functional groups [153]. Curcumin is an amphipathic molecule with the central and neighboring regions are polar in nature with a methine segment (lipophilic) separating them **(Figure 1b)**. Three main functional groups in curcumin comprises of two aromatic ring systems with o-methoxy phenolic groups, and one beta-diketone moiety (alpha beta-unsaturated) [154, 155]. The structure of curcumin plays a key role in its release behavior in different medium. However, both internal and external stimulus are responsible for the release kinetics of curcumin from alginate hydrogels.

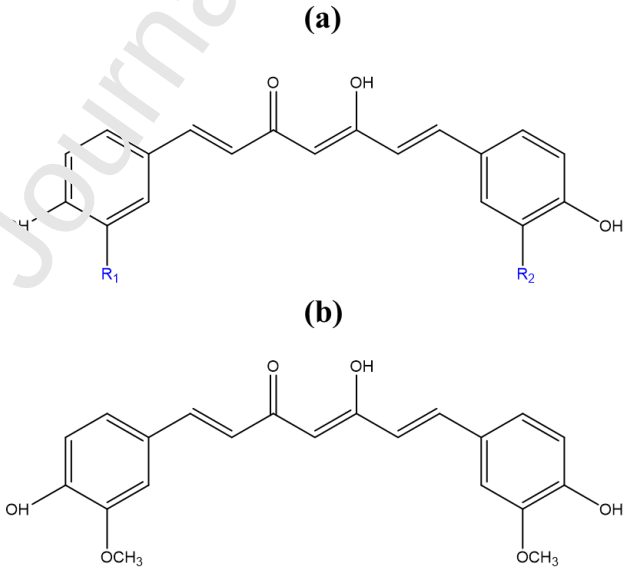

Figure 1 Molecular structure of (a) Curcuminoids, and (b) Curcumin

4.1 External stimulus

4.1.1 pH

It is well known that pH plays a vital role in controlling the release behavior of any drug from the designed system. In case of curcumin varying pK_a values are reported which depends on the method of estimation and the solvent in use [156]. Curcumin is known to exhibit *keto-enol* tautomerism in aqueous solution with the *enol* form being more stable in the solid phase. Moreover, subject to the solvent in use, up to 95% curcumin could exist in the *enol* form [157]. Here, the *keto* form acts as an effective proton donor, while the *enol* form acts as a strong electron donor [154]. In is to be noted that the *keto* form is dominating under acidic and/or neutral conditions, whereas under alkaline conditions, the enolate form is more dominating [158]. The release of curcumin from alginate hydrogels remarkable depends on the solvent system used and the method of encapsulation.

Curcumin are known to be more stable in acidic environment which could be accounted for its conjugated diene structure. However, in aqueous solutions and at an alkaline pH, deprotonation at the acidic phenol group in curcumin takes place resulting in the formation of phenolate ion(s) and demolition of the native structure [159]. The release of curcumin from the alginate-based hydrogel greatly depends on the pH conditions of the design as the fate of the degradation, stability, and release of curcumin from the hydrogel network depends on it. Curcumin comprises of three *pKa* values of acidic protons with pKa_1 of 7.8 corresponding to the dissociation of enol proton, and pKa_2 and pKa_3 of 8.5, and 9.0, corresponding to the dissociation of the phenolic protons, respectively [160, 161]. In case of alginate hydrogels, the degree of swelling at different pH also effects the drug release behavior from these hydrogels, as indicated by Shi *et al* where low amount of drug release was observed in case of alginate hydrogel beads at acidic pH [162]. Further, t low pH the hydration of alginic acid

directs the formation of acid gels which are highly viscous in nature [163]. This in turn effects the release of drug from alginate hydrogel network.

In case of wound healing, the intracellular and extracellular pH regulates the healing process as it is well documented that the different stages of wound healing are in coherence with changing pH of the surrounding microenvironment [164, 165]. Further, it is been demonstrated that the most effective wound healing transpires at acidic pH, while wounds with alkaline environments have been associated with chronic wounds [166]. Moreover, the milieu around tumours are often associated with acidic conditions [167]. Thus, the pH conditions in which the hydrogel is holding curcumin and the environment in which curcumin will be release could be flagged as a governing factor for tehri release.

4.1.2 Temperature

Drug release mechanism from a hydrogel carrier depends on many factors which includes but not limited to bonding pattern between the drug and carrier, drug carrier interaction, drug carrier deformation [168, 169]. One important aspect in the drug release phenomenon is the temperature gradient between its internal architect and external environment. With the advancement in the field of hydrogels, temperature responsive hydrogels have gained considerable attraction. These hydrogels have two distinct forms, it remains in liquid state in one particular temperature and offers gelation at a particular temperature. The release of drug is affected due to tis gelation process [170]. Further, degradation of the structural network of the hydrogel could also enhance the release of curcumin, which in turn is affected by the temperature resistance of the hydrogel network.

The swelling behavior of hydrogels is a sensitive feature which is also a crucial parameter in terms of the drug release behavior of the designed hydrogel which is a temperature dependent

property. Further, changes in the temperature also governs the transition of volume of hydrogels, which shows substantial behavior in drug release profile [171, 172]. The solubility of curcumin has always been a matter of concern for its wide spread biomedical applications. It is to be noted that temperature plays a vital role in increasing its aqueous solubility with an increase in the solubility over twelve folds upon heating [173]. Further, curcumin exhibits more aqueous stability when designed in the form liposomes compared to the free curcumin at 25℃ [174]. The effect of temperature can also be seen on the degree of crosslinking which again is a key parameter that governs the release of drug from hydrogels. Gelation temperature significantly effects the rupture strength of hydrogels, which influences the release of drug that is partitioned between the crosslinked hydrogel networks. Temperature changes have always been a sensitive issue while designing a pharmaceutical molecule for clinical applications as the change in temperature directs the release profile of a drug.

4.2 Internal stimulus

4.2.1 Porosity

Hydrogels consists of a 3D network of crosslinked hydrophilic polymers dispersed in water, thus are sometimes referred as colloidal solutions [175]. The expulsion of drug from a hydrogel is affected by both intrinsic as well as extrinsic factors like pH, temperature, crosslinking rate, viscosity, dielectric properties, porosity etc. [176]. Though all these properties play their individual roles in determining the drug release rate, porosity of the hydrogels is an essential feature in terms of regulating drug release behavior as the impact of water is mostly highlighted in case of pore formation including the pattern of pore formation along with its size distribution [177].

Porosity is a distinctive feature that influences many of the critical aspects of a hydrogel as it

can help in predicting the rate of deformation of a hydrogel during compression, pharmacokinetic behavior across the system of administration, shelf life, degradation rate, penetration of moisture content, and volume/area available for drug to captured inside the hydrogel. All these factors are prerequisite in determining the rate and outline of drug release from the hydrogel network. Whenever a hydrogel-based drug delivery system comes in close interaction with the suitable dissolution medium, the release of drug to the respective medium follows two distinct procedures first is the dissolution of drug molecules from the surface or across the pores filled with water and second is by diffusion of drug via water filled channels [178]. The adsorption rate of drug and its release from the hydrogels could be burst release or can follow sustained release pattern which in turn depends on the surface properties and the polarity of the solvent medium [179, 180].

The release of drug molecule for a pore is also affected by the type of pore present in the system. Mainly three type of pores are in common namely open, closed and transport [181]. The pore which connects the external surface to the materials interior via passing through the material internal architect is known as open pore whereas if the pore is present in the internal structure of the system without any connection to the external is known as closed pore. The pores which are interconnected from the external to the inside of the system and also are connected to the blind pores (dead end pores inside the system) are known as transport pores. The distribution of these pores inside a hydrogel is collectively known as porosity and the percentage occurrence of these pores regulates the dissolution, diffusion and release of drug molecules from the hydrogel structures.

4.2.2 Mesh size

The open spaces between the crosslinked polymer chains in case of hydrogel is known as

meshes and it plays a crucial role in governing the diffusion of drugs from the polymer network. The size and arrangement of these meshes depends on many factors including the concentration of polymers and crosslinking agent, temperature, pH. Moreover, the typical mesh size for hydrogels have been reported to be in the range of 5 to 100 nm [182, 183]. This wide range in the mesh size could be associated with the diverse nature of polymers and heterogeneity in the polymer network formation [184]. The diffusion pattern followed by drug molecules from the hydrogel network largely depends on the mesh size as it is responsible to regulate the steric interactions amid the polymeric chains present in the hydrogel and drug molecules [185]. If the mesh size is large compared to the drug molecules entrapped then the drug release process is directed towards diffusion. Whereas, in case of small drug molecules, the movement is independent of mesh size and the drug release is fast. Here the diffusivity is governed by Stokes Einstein equation as [182].

$$D = \frac{RT}{6\pi\eta r}$$

Where:

R stands for gas constant, T is absolute temperature, η stands for the viscosity of the solution, and r is the radius of the drug molecule.

It is to be noted that when the mesh size and the radius of the drug molecule tends to get very close the steric hindrance effect on diffusion of drug molecules becomes substantially pronounced. To regulate the release of drug molecules from the hydrogel network, the mesh size can be controlled by changing the concentration of polymers and crosslinking agents. Typically, the mesh size reduces with increase in the concentration of cross-linkers and polymers. In this case, significant frictional drag is experienced by the diffusing drug

molecules, and as there are patches in the polymer network where the mesh size is smaller than the drugs, increase in the path length for drug transport is observed which results in slow drug release [186]. Further, if the mesh size is very small compared to the drug molecules, strong steric hindrance is experienced by drugs due to which the drug molecules remain entrapped inside the polymeric network with restricted release movements **(Figure 2)**.

The typical release behavior of drug molecules from the hydrogel network is governed by many factors and in order to attain the desired release profile of drugs from the hydrogel, the selection of the polymer type and cross-linkers along with their concentration is very important as this regulates the mesh formation and their size distribution. The choice of drug molecule together with its intrinsic character and interaction approaches with the polymer network also plays a substantial role in their release.

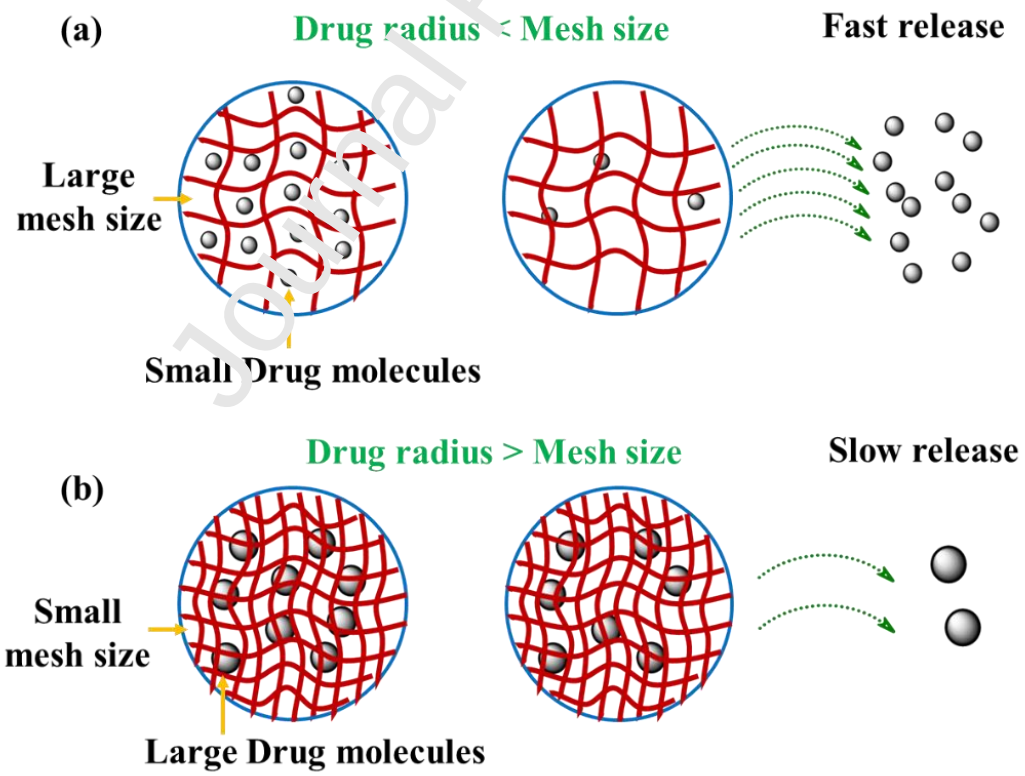

Figure 2. Release behavior of drug molecules from the hydrogel network in two scenarios (a)

Radius if the drug molecule is less than the mesh size, and (b) Radius if the drug molecule is less than the mesh size

4.2.3 Degree of Crosslinking

Hydrogels are known to absorb huge amount of water and displays exclusive swelling behavior without being dissolved in the aqueous environment. This unique behavior of the hydrogels is due to the presence of crosslinkers inside the hydrogels network. These crosslinkers provide stability and resistance against breakage to a hydrogel. The crosslinking in a hydrogel networks are provided by covalent bonding, hydrogen bonding, and Vander Waals interactions [187]. Crosslinking in a hydrogel network is mainly formulated through chemical or physical crosslinking [188]. Physical crosslinking in hydrogels involve external stimulus-based chain crosslinking with the help of light or temperature, physical entanglement using ion interactions, and block and graft copolymerization while chemical crosslinking in hydrogels involves covalent or coordinate bonding between polymeric chains [189]. The degree of crosslinking is directly related to the swelling behavior. It has been observed that the diffusion of water in case of glassy polymers often deviates from the Fick's law predictions, guided towards non-Fickian diffusional behaviour. This deviation from the Fick's law predictions is often linked with the degree of rearrangements made in the hydrogel assembly to hold maximum water. Hence, two different phenomenon of drug transport mainly Fickian and non-Fickian are observed across a hydrogel network which in turn depends upon the swelling behaviour and transport of water and drug molecules [190, 191].

The rate of drug release from a hydrogel depends on many aspects of crosslinking which includes the extent of crosslinking, type of crosslinker, concentration of the crosslinking agents, and the rate of gelation. Tailoring the crosslinking stratagems is a crucial selection for

altering the physical, mechanical and drug release pattern of a designed system [192]. The release behaviour of drug is also affected by the degradation or the hydrogels or breakage to the cross linkers. This is a very attractive strategy that allures many researchers to design drug loaded hydrogels that can exploit the surrounding conditions across a pathological ailment like cancer [193, 194] and wound management [195, 196].

5. Application of curcumin loaded alginate hydrogels

The use of alginate-based hydrogel dressings accelerated wound closure, improved re-epithelialization, enhanced ECM remodeling, and increased nerve re-innervation when compared to an off-the-shelf synthetic treatment. In addition, blending bioactive hydrogels such as gelatin and collagen or nanomaterials with alginate hydrogels provide an effective platform for smart delivery systems as they can be loaded with cells, antimicrobial agents, and growth factors for controllable topical administration [197-199].

5.1 Wound healing

Alginate hydrogels have been utilized as a potential candidate for wound healing applications due to their biocompatible and porous behaviour, higher water content, and permeation-enhancing abilities to both water and gas [200]. In this section, we have discussed the literature highlighting the wound-healing applications of curcumin-loaded alginate hydrogels and their modified forms with the usage of co-polymeric networks.

In order to explore the potential of alginate-based hydrogels in wound healing, Zakerikhoob *et al.* fabricated curcumin encapsulated sodium alginate grafted poly(N-isopropyl acrylamide)-based (CUR-SA-PNIPAM) thermosensitive hydrogels. CUR-SA-PNIPAM exhibited thermo-gelation between 27-42 °C based upon the concentration of the copolymers,

pNIPAM chain length and pH of the medium. CUR-SA-PNIPAM significantly prolonged the release of curcumin up to 72 h with superior stability. Further, CUR-SA-PNIPAM was tested at *in vivo* levels where improved therapeutic potential was achieved through enhanced rate of wound contraction, reduced inflammation, and enhanced collagenases leading to an increase in fibroblast counts [201]. In another study, researchers fabricated SA-chitosan (CS) hydrogels loaded β-cyclodextrin (β-CD) inclusion complexes with varying concentrations of calcium chloride ($CaCl_2$; cross-linking agent) for effective delivery of curcumin. It was observed with an increased concentration of $CaCl_2$ increased the mechanical properties however reduced water swelling, moisture absorption, and weight loss. The hydrogels inhibited bacterial growth of both *Escherichia coli* (*E. coli*) and *Staphylococcus aureus* (*S. aureus*). The hydrogels were found to be non-toxic to NCTC-cloned 929 cells as well as normal human dermal fibroblast cells, thus could be used as a potential strategy for wound dressing application [202]. Further, Mohammadi *et al.* studied the formation of *in-situ* hydrogels by grafting (2-Hydroxy isopropyl)-β-cyclodextrin (HPβCD) inclusion complex with sodium alginate (SA) for effective delivery of curcumin (CUR-SA-HPβCD). The formed complex exhibited higher encapsulation efficiency (% EE; 88.2 %). Further, the formed hydrogel of CUR-SA-HPβCD was helpful in preventing the agglomeration of curcumin alongside the formation of uniform nanosized particles. The fabricated CUR-SA-HPβCD hydrogel exhibited higher water uptake and improved the cumulative release of CUR (80 % over 72 h) with enhanced cytocompatibility, essential for wound healing applications. The CUR-SA-HPβCD showed potential antibacterial effects against methicillin-resistant *S. aureus* and *Pseudomonas aeruginosa* (*P. aeruginosa*) [203].

In another study, researchers developed CS-SA super-porous hydrogel incorporated with CUR and honey using an in-situ polymerization technique, further used for the formation of

biodegradable sponges. The essential formulation factors were optimized using a 3^2-factorial design. The optimized formulation showed higher swelling capacity, tensile strength, *in-vitro* drug release, bio-adhesion, and moisture transmission. They also induced tissue granulation and re-epithelialization with high higher wound healing capacity and tissue contraction. The *in vivo* wound healing ability for the designed hydrogel was evaluated for a period of seven days and was compared with a control group administered with provident ointment, where substantial wound closure was witnessed for the designed hybrid hydrogel system [204]. As a future clinical utility, it was also highlighted that the optimized formulation can be a potent candidate for the treatment of diabetic foot ulcers.

On similar grounds, *Albarqi et al.* fabricated CS-SA based hydrogel membranes loaded with curcumin via microwave-assisted cross-linking method and evaluated its wound-healing potentials. In this case, the *in-vitro* results showed substantially improved swelling ability, decreased erosion, and established smoother surfaces with optimum drug content all accounted for the microwave assisted methodology. Here, superior tensile strength of the designed hydrogels was recorded with sustained release of curcumin (41 ± 4.2% within 24 h). Further, the *in-vivo* results demonstrated that the drug-loaded hydrogel increased the percent re-epithelialization with a greater extent of collagen aggregation ensuing in the distinct formation of epidermal and stratum corneum layers [205].

The re-epithelialization of epidermal layer along with accelerated collagen deposition is a vital attribute for efficient wound management. In this regard Li *et al.* developed curcumin containing-nanocomposites (CNs) composed of curcumin, methoxy poly (ethylene glycol)-b-poly(ε-caprolactone) copolymer and further loaded the CNs into N, O-carboxymethyl CS, and oxidized alginate (CS-OA-CNs) to form an *in-situ* complex hydrogel system. Here,

sustained release of curcumin from the developed injectable hydrogels was observed with diffusion-controllable behaviour in the initial stages followed by erosion behaviour towards the end phase. The *in-vivo* results further confirmed the potential of this hydrogel in wound healing specially in the dorsal wounds of treated rats along with enhanced the re-epithelialization of the epidermal layers and collagen deposition within the wounded tissue [206].

Chondroitin sulfate (CS) has been a potent candidate in wound management. Thus, in order to explore the potential of CS Shah *et al.* synthesized chondroitin sulfate (CS) and SA-based injectable hydrogel through solvent casting method and further co-loaded with curcumin and stabilized with the addition of pluronic PF-127. The complex hydrogel formulation synergistically assisted in re-epithelization, enhanced angiogenesis, and collagen aggregation at the wound microenvironment. Formulation exhibited a controlled drug release profile for encapsulated drugs, and exhibited superior biocompatibility, confirmed through *in-vitro* studies against 3 T3-L1 fibroblasts cells and *in-vivo* toxicity studies in subcutaneously administered animal models [207]. Further, in another study, a hybrid nanosized scaffolds was designed that was composed of collagen-SA-based hydrogels and curcumin-CS NPs **(Figure 3)** [208]. These hybrid scaffolds demonstrated improved biocompatibility, better water uptake, improved solubility, and stability, as well as the release behaviour of CUR. Upon administration of the synthesized hybrid scaffolds at *in-vivo* levels, significantly enhanced wound contraction rate was observed. In addition, the animals treated with the hybrid scaffolds exhibited complete epithelialization with the development of abundant granular tissues.

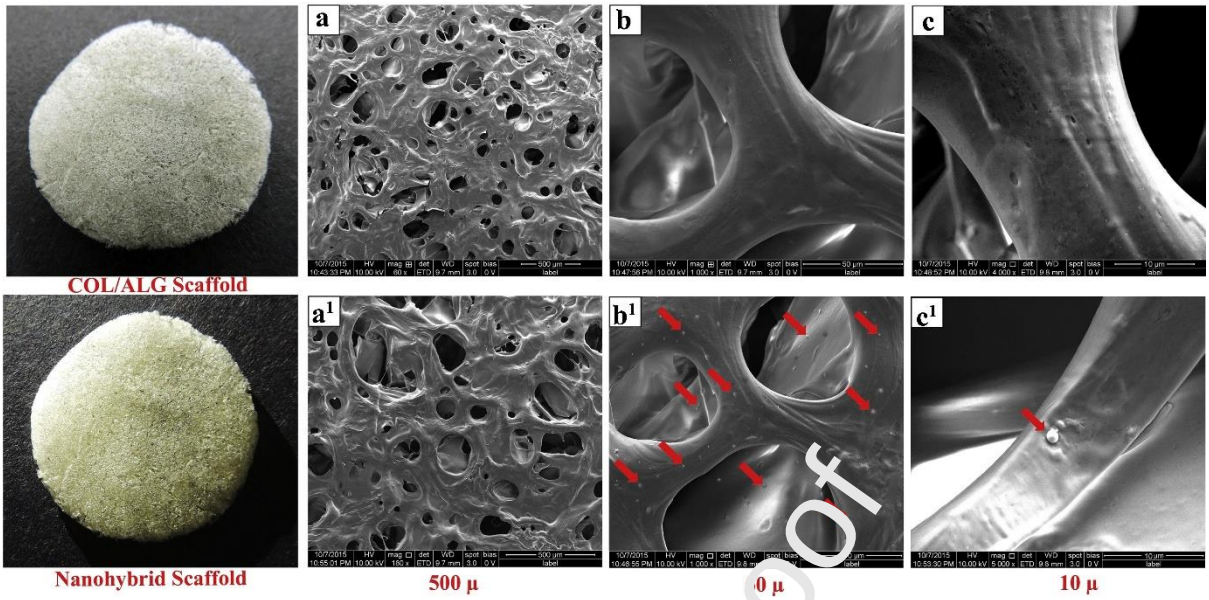

Figure 3. SEM images of (a-c) collagen/alginate (COL/ALG) scaffolds (no nanoparticles) and (a^1-c^1) COL/ALG scaffolds with curcumin loaded chitosan nanoparticles (nanohybrid scaffold). Adapted with permission from ref. [208]

There are many polysaccharides that are used in combinations and as individuals for wound management, one of which is carrageenan. Taking this into consideration, Postolovic *et al.* developed a carrageenan-SA-poloxamer 407 (P407)-based hydrogels incorporated into films for the dual drug delivery of diclofenac (DF) and curcumin for wound healing applications. Three different hybrid films were fabricated including DF-loaded film, curcumin-loaded film, and dual drug loaded (DF/curcumin) film. With improved % EE for both the drugs the synergistic effect of the two drugs were observed. Further, DF/curcumin-co-loaded hybrid films also exhibited antibacterial activities against both *Bacillus subtilis* and *S. aureus* and operated as a multifunctional therapeutic agent for treating inflammation, reducing pain, and enhancing wound healing progression [209]. In the area of wound healing hydrogels have been constantly in use. In another study, researchers prepared pickering emulsion-hydrogel nanocomplex systems composed of curcumin, SA, and carboxymethyl chitosan (CMCS)

stabilized with P407 [210]. The effect of ionic concentrations and temperature on the appearance and average diameter of the synthesized pickering emulsion hydrogel was also studied **(Figure 4)**. The pickering emulsion assisted in the controlled release of encapsulated drug. These nanocomplex hydrogels exhibited antibacterial activities against *E. coli* and *S. aureus* and enhanced wound healing as confirmed by increased levels of Ki67 and CD31 expressions, mRNA levels of TGF-β3, and decreased mRNA levels of α-SMA and TGF-β1.

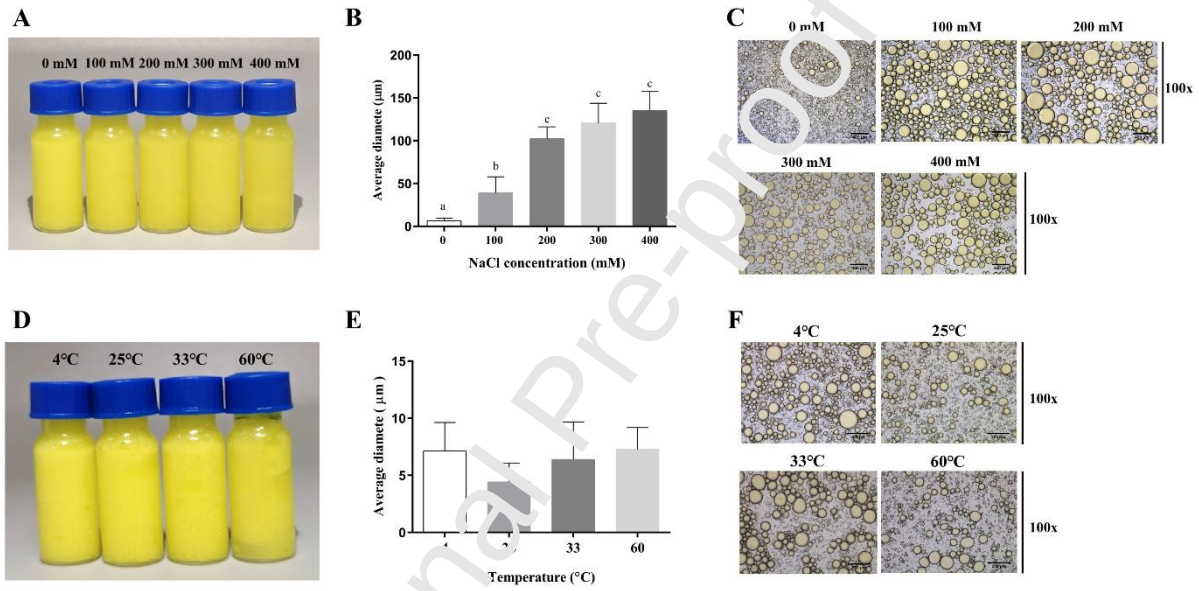

Figure 4. Effect of NaCl concentration and temperature on the appearance (A, D), average diameter (B, E) and optical microscope images (C, F) of carboxymethyl chitosan-sodium alginate stabilized pickering emulsion hydrogels. Statistical relevance at ($P < 0.05$). (Magnification 100×). Adapted with permission from ref. [210]

In order to take advantage of the dual loading and synergistic effect, Comotto *et al.* functionalized alginate-based hydrogel for effective delivery of curcumin and t-resveratrol that showed superior mechanical properties and high oxygen permeability. Upon *in-vitro* analysis, the drug release exhibited burst release initially followed by sustained release from t he alginate hydrogel network. The hydrogel exerted superior biocompatibility,

conformed through cytotoxicity assessment against human keratinocytes **(Figure 5)**. The formulation also exhibited potential antibacterial activity against *S. aureus* [211].

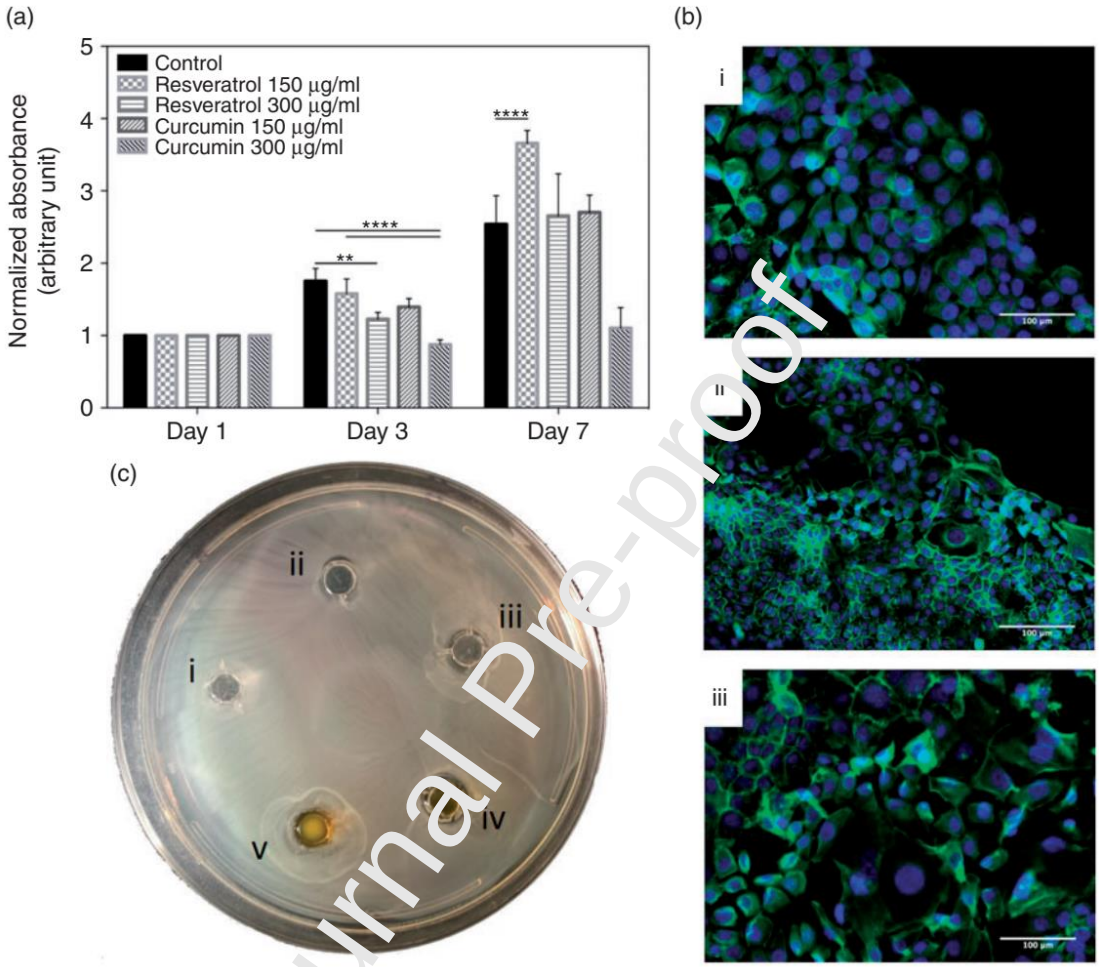

Figure 5. Cellular activity and antimicrobial nature of the drug loaded hydrogels. (a) Metabolic activity of keratinocytes upon treatment with hydrogels in varied concentrations of drugs. (b) Fluorescent micrographs of F-actin (green) and DAPI (blue) staining of keratinocytes (i) control (ii) cultured with 150 µg/mL each of t-resveratrol, and (iii) curcumin, respectively. (c) Antimicrobial activity against *S. aureus* against hydrogel with (i)150 µg/mL and (ii) 300 µg/mL of t-resveratrol, (iii) 150 µg/mL and (iv) 300 µg/mL of curcumin (Scale bar: 100 µm) (**p < 0.01 and ****p < 0.0001). Adapted with permission from ref. [211]

Moreover, Zhang *et al.* developed a hybrid hydrogel system composed of curcumin, epigallocatechin gallate (EGCG), hyaluronic acid (HA), SA, and polylysine (PLL) for the effectively manage irradiation-induced skin injury [212]. Five different hydrogel formulations were designed and tested for their hemocompatibility, adhesion with fresh blood and hemolysis ratio **(Figure 6)**. These fabricated hybrid hydrogels exhibited anti-biofouling effects by efficiently resisting protein and bacterial adhesion along with evading immune responses. Further, the synthesized hybrid hydrogel showed sustained release behaviour for both curcumin and EGCG, and significantly accelerated the healing process of the injured skin by improving anti-inflammatory and anti-oxidative effects, and indorsing angiogenesis.

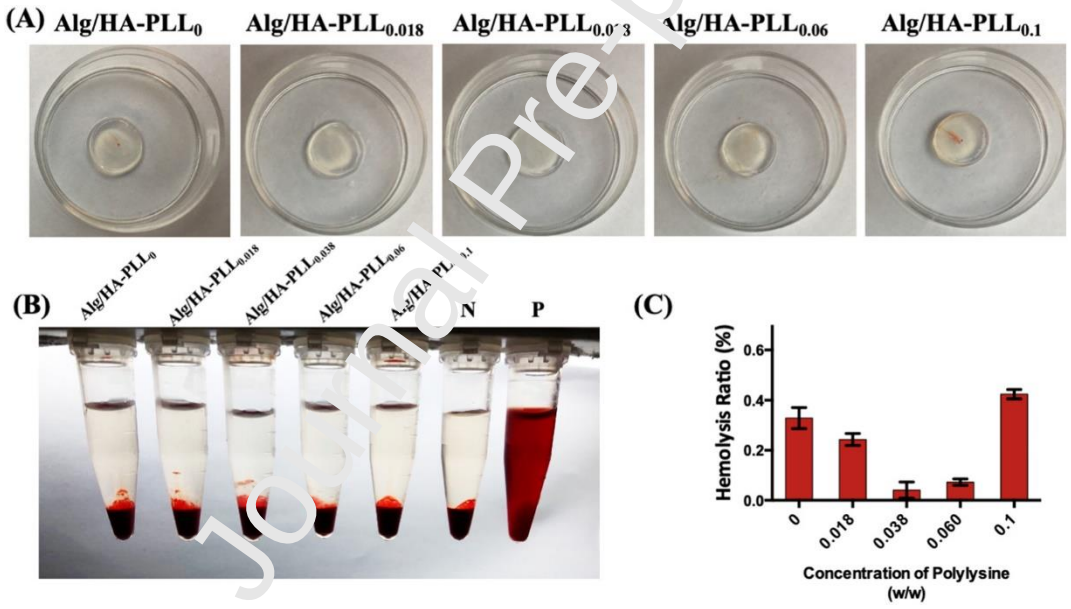

Figure 6. (A) Hemocompatibility analysis of five differently charged hydrogel formulations, (B) Adhesion tests of fresh blood cells on the surfaces of different hydrogel formulations, and (C) Hemolysis ratios of the hydrogel samples. Adapted with permission from ref. [212]

In another study, researchers developed curcumin nanoparticles-loaded CS-polyvinyl alcohol-SA-based hydrogels functionalized with mesoporous Ag_2O/SiO_2 for transdermal

usage. The effect of mesoporous Ag_2O/SiO_2 on the stability and drug loading ability of hydrogels was evaluated with varying research concentrations and was demonstrated that upon increasing the concentration of Ag_2O/SiO_2 significantly increased the mechanical strength and healing properties of the designed system. The hybrid formulation exhibited potential wound healing effects and antibacterial activity against *Staphylococcus epidermidis*, *Acinetobacter baumannii* and *Proteus mirabilis* [213]. In another study on wound management, Nguyen *et al.* developed curcumin loaded topical hydrogel formulation conjugated with calcium SA-based nanocarriers (CSNs), developed using nanoemulsification-polymer crosslinking technique. CSNs exhibited a hydrodynamic size distribution of ~200 nm with a surface charge of ~ - 30 mV, along with its superior biocompatible nature. Curcumin loaded CSNs showed improved % EE (~95%), with potential antioxidant effects. Human skin treated with CUR-loaded CSNs demonstrated substantial accumulation of the CUR in the upper skin layers, ensuring the potential applications of these hydrogel-based nanocarriers in wound healing, and cosmeceutical applications [214].

In order to develop an efficient hydrogel system for wound management, several factors have to be accounted for which not only includes the drug encapsulation and release behaviour but also the pattern of degradation of the drug, the degradability of the hydrogel system, its level of biocompatibility along with its mechanical and physicochemical attributes. The combination of curcumin loaded alginate hydrogels are not only cost-effective, but also provide a platform where, this system could be functionalized and manoeuvred based on the targeted application. The compatibility of this design with the biological system provides opportunities to further improve the efficiency of this combination by incorporating multifunctional arrangements.

5.2 Cancer Therapy

Alginate based hydrogels have shown significant potential in many biomedical applications including cancer treatment due to its ability to store high-water content, nontoxic nature, excellent biocompatibility, and biodegradability which allows them to act as an apt transported to carry chemotherapeutic drugs and other biomolecules (proteins and genes) to the target site [215]. Further it should be noted that in case of alginate-based hydrogel systems, the drug release behaviour from the architectural network of the hydrogel is mainly achieved through diffusion-mediated, swelling-mediated, chemically-mediated, and environment-responsive releases [216]. This section summarizes the research work specifically focused on the anticancer capability of curcumin-loaded alginate hydrogels.

In order to explore the potential of cancer treatment by curcumin loaded alginate-based hydrogels, Abbasalizadeh *et al.* fabricated curcumin and chrysin-loaded SA-CS hydrogel system (CCSCHs) using an ionic-gelation technique applying $CaCl_2$ and evaluated the potential anticancer effects against breast cancer (T47D) and lung cancer (A549) cells. Results showed that the designed hydrogel system (CCSCHs) substantially lowered the population of viable cells and induced apoptosis in case of both the treatment groups. Moreover, cell cycle studies showed that CCSCHs caused cell arrest at G2/M phase in both cell lines [217]. In another study, Afzali *et al.* synthesized SA-CS- β-CD-based hydrogels for encapsulating curcumin, further conjugated with folic acid to achieve active targeting ability. Further, the *in-vitro* cytotoxicity studies demonstrated that nanosized (155 nm) curcumin-loaded hybrid hydrogels exhibited potential anticancer activity against Kerman male breast cancer (KMBC-10) cells in a dose-dependent manner with active targeting ability. Moreover, formulation significantly inhibited cell proliferation and augmented apoptosis in the spheroid carcinogenic cells. cancer cells [218].

On similar goals for cancer treatment, Wang *et al.* developed an *in-vitro* 3D co-cultured tumor-vascular barrier (3D-TVB) model using SA hydrogel beads and the Transwell system. Initially, the SA-hydrogel beads were encapsulated with prostate cancer (PC-3) and fibroblast (NIH/3T3) cells that were further cultured in the bottom of the Transwell chamber. On the other hand, human umbilical vein endothelial cells (HUVECs) were cultured over the permeable membrane in the upper cavity to arrange a vascular barrier. Finally, curcumin response of the 3D-TVB model to was evaluated and it was observed that as compared to the 2D-TVB, the 3D-TVB model highest activity against the cancer cells [219]. The study emphasized on the utility of microfluidic models for recapitulating the cancer microenvironment to get real time and accurate information on the treatment process of cancer.

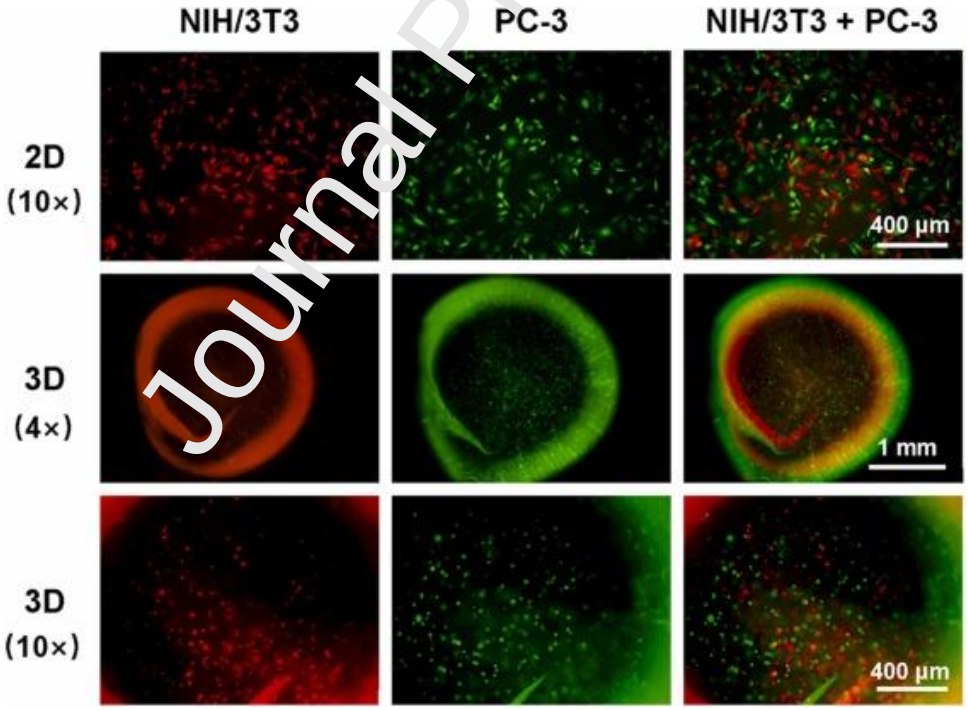

Figure 7. Two dimensional (2D) coculture model and three dimensional (3D) coculture spheroid model of NIH/3T3 and PC-2 cells demonstrating the internalization of VE-cadherin. Scale bars: 1 mm (4×), 400 µm (10×). Adapted with permission from ref. [219]

Further, researchers prepared graphene oxide (GO)-loaded curcumin nanosheets encapsulated SA-hydrogels, cross-linked with Ca^{2+}, to form hybrid hydrogels and evaluated its potential anticancer effects against squamous cell carcinoma (SCC)-affected regions. It was further demonstrated that the presence of GO helped in increasing the stability in aqueous media by countering the de-crosslinking procedure of the polymeric network. Moreover, the *in vitro* cytotoxicity evaluation of the designed system demonstrated that lower concentrations of curcumin (2.5% and 5 % wt) significantly reduced the inherent toxicity of GO against the healthy cells, while higher concentrations were ineffective owing to the inculcation of antioxidative/pro-oxidative features. In addition, sustained release of curcumin was recorded from the designed hydrogel system along with cytotoxic effect against SCC cancer cells [220].

Further exploring the ability of curcumin and alginate-based hydrogel system, Wezgowiec *et al.* developed micro- and macroparticles of curcumin loaded to SA-based hydrogels and evaluated its effectiveness against human colon cancer cells (LoVo). Further, the synergistic effects of polymeric (CS and gelatin) coating of curcumin-loaded micro/macroparticles were assessed. It was demonstrated that comparatively less amount of drug was encapsulated in the microparticulate system compared to the microparticulate systems along with sustained drug release in the later. Negligible cytotoxicity was observed against LoVo cells in case of empty particulate system, while the curcumin loaded particulate system reduced the viable cell population of the LoVo cells (higher for microparticles than macroparticles) with gelatin-

coated or uncoated microparticles being highlighted as the most potent carriers [221]. In another study, researchers fabricated pH-sensitive interpenetrating polymeric network (IPN) hydrogels composed of SA-g-poly(N-acryloyl-L-phenylalanine), ethylene glycol vinyl ether and, hydroxyethyl acrylate (HEA) by utilizing free radical polymerization. The synthesized hydrogels were encapsulated with curcumim (*in-situ*) [222]. The histopathology of the designed curcumin loaded hdyrogels were analysed and compared with control and pure curcumin drug **(Figure 8)**. Curcumin loaded hydrogels demonstrated an EE of 75% along with antiproliferative activity against human breast cancer (MCF-7) and human hepatic (HepG2) carcinogenic cells compared to free drug. Additionally, the anticancer effects of curcumin loaded hydrogel was also explored at *in vivo* levels

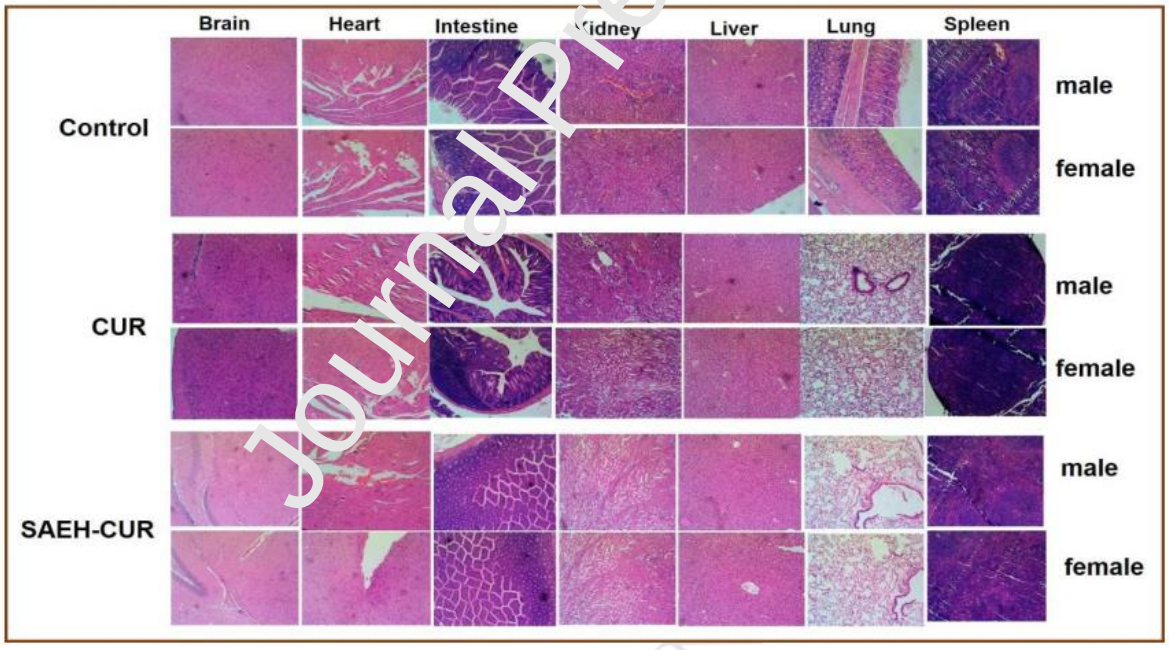

Figure 8. Histopathology analysis of Control, curcumin (CUR), and curcumin loaded sodium alginate-g-poly(N-acryloyl-L-phenylalanine (CUR loaded SAEH). Adapted with permission from ref. [222]

Hydrogels are an ideal platform for drug transport across a cancerous tissue because of their protective sense and convenient handling [223]. Apart from being utilized as a carrier platform hydrogel can also be utilized as extra cellular matrix (ECM) implicating 3D cell culture environment [224]. The porous nature and the interconnectivity inside the hydrogels network directly influence the cellular behaviours such as cell attachment, proliferation, migration, differentiation etc. These are some vital features that needs to be addressed for an effective and efficient cancer therapy. **Table 1** summarizes the research work concerning curcumin loaded alginate hydrogel matrix for wound healing and cancer therapy.

Table 1: Summary of curcumin loaded alginate hydrogels with details of the crosslinking methods and crosslinkers used along with vital features across wound healing and cancer therapy.

Polymers	Crosslinking method	Crosslinking agent	Drugs/Biomolecules	Applications	Major Outcomes	Ref.
PNIPAM, SA	Physical (co-polymeric grafting), Thermo-responsive cross-linking	PNIPAM	CUR	Wound healing	• Prolonged release of CUR • ↑wound contraction • ↓inflammation, • ↑collagenesis • ↑number of fibroblasts	[201]
SA, CS, HPβCD	Chemical, inclusion complex-based cross-linking	$CaCl_2$, Glutaraldehyde solution	CUR	Wound healing, Anti-bacterial	• ↑drug release • ↓growth of both *E. coli* and *S. aureus* • no cytotoxicity (NCTC clone 929 cells and fibroblast cells)	[202]
SA, HPβCD	Chemical, inclusion complex-based cross-linking	-	CUR	Wound healing, Anti-bacterial	• ↑encapsulation efficiency and drug release • Uniform particle size with high stability • ↓methicillin-resistant colonies of *S. aureus* and *P. aeruginosa* • Cytocompatible	[203]
SA, CS	Physical, in-situ polymerization	SA, CS, acrylamide	CUR, Honey	Wound healing	• ↑swelling capacity, tensile strength, drug diffusion, bio-adhesion, water content transmission • ↑tissue granulation and re-epithelialization • ↑wound contraction with faster wound healing	[204]

					abilities	
SA, CS	Physical, Microwave-assisted cross-linking	CS, SA	CUR	Wound healing	• ↑encapsulation efficiency and drug release with sustained release behavior • ↑swelling ability • ↓erosion • ↑re-epithelialization and collagen deposition	[205]
CMCS, MPEG-PCL	Physical, Simple-mixing	-	CUR	Wound healing	• Initial burst release followed by sustained release of drug • ↑wound healing abilities • ↑re-epithelialization of epidermis and collagen deposition over wounded tissues • ↑process of wound healing	[206]
CS, SA	Physical, In-situ polymerization, Chemical cross-linking	P127; P188, $CaCl_2$	CUR	Wound healing	• ↑tissue regenerative ability and wound healing • ↑bioavailability • Biocompatible • ↑fibroblasts-like cells • ↑collagen deposition • ↑distinguished keratinocytes	[207]
CS, SA, Collagen	Physical scaffold development, Chemical cross-linking	PVP-K30, STPP, EDC, NHS, MES, collagenase	CUR	Wound healing, Anti-inflammatory	• ↑bioavailability • Sustained drug release • ↑water uptake and biocompatibility • ↑wound contraction with faster wound healing	[208]

					abilities • ↑epithelialization with the formation of thick granular tissues • ↓inflammation	
SA, κ-carrageenan	Physical (Polymeric films using casting method), Chemical (cross-linking)	P407, $CaCl_2$	CUR, Diclofenac	Wound healing, Anti-bacterial, Anti-inflammatory	• ↑bioavailability with high encapsulation efficiency • Wound contraction with faster wound healing abilities • ↑antibacterial activity against *B. subtilis* and *S. aureus* • ↓inflammatory phase and pain	[209]
CMCS, SA	Physical (pickering emulsion), Chemical (cross-linking)	P407	CUR	Wound healing, Anti-bacterial	• ↑stability and solubility • ↑bioavailability • ↑ levels of Ki67 and CD31 and mRNA levels of TGF-β3 • ↓α-SMA and TGF-β1 • ↑wound contraction • ↑antibacterial activity against *E. coli* and *S. aureus*	[210]
SA,	Chemical (cross-linking)	$CaCl_2$, glycerol	CUR, t-resveratrol	Wound healing, Anti-bacterial, Anti-inflammatory	• Burst release followed by the sustained drug release • ↑ mechanical properties, water uptake, and oxygen permeability • ↑antibacterial activity	[211]

					against *S. aureus* • Biocompatible, no toxicity against human keratinocytes • ↑anti-inflammatory response	
SA	Chemical (cross-linking)	Polylysine	CUR, HA, EGCG	Wound healing, Anti-biofouling, Anti-inflammatory	• ↑solubility and drug loading, • ↑ mechanical properties, water uptake • Sustained drug release • ↓skin injury • ↑healing process by ↑ ROS scavenging and promoting angiogenesis • ↑anti-inflammatory response	[212]
SA, CS	Physical (metallic nanoparticles); Chemical (cross-linking)	PVA, sodium silicate, silver nitrate	CUR	Wound healing, Anti-bacterial	• Sustained drug release • ↑ mechanical properties, water uptake • ↓bacterial growth of *A. baumannii*, S. epidermis, and *P. mirabilis* • Biocompatible • ↑wound healing process with anti-inflammatory actions	[213]
SA, CS	Chemical (cross-linking)	$CaCl_2$	CUR, Chrysin	Anticancer	• ↑solubility, drug loading, and stability • ↑bioavailability • ↓cell viability and	[200]

					proliferation of T47D and A549 cells • G2/M phase cell cycle arrest in both A549 and T47D cells	
SA, CS, βCD	Chemical (ionotropic gelification)	STPP	CUR, FA	Anticancer	• Spherical nanoparticles (155 nm) • Folate receptor-targeted drug delivery into spheroids • Dose-dependent anticancer effects against KMBC 10 cells • ↓CXCR4 expression • ↓cell proliferation and ↑cellular apoptosis • Biocompatible with negligible toxicity	[218]
SA	Chemical (cross-linking)	$CaCl_2$, GO	CUR	Anticancer	• ↑solubility and drug loading • Sustained drug release • GO ↑stability in aqueous media • CUR ↓intrinsic toxicity due to GO against healthy cells • ↑cytotoxicity against SCC cells	[220]
SA, gelatin, CS	Physical (micro-/macro-particles formation) Chemical (cross-linking)	$CaCl_2$	CUR	Anticancer	• ↑solubility and drug loading • ↑mechanical properties and moisture uptake • ↑concentration of ALG ↑roughness and swelling	[221]

					index of macroparticles • structural configuration of particles exhibited a significant role in regulating drug release behavior • CS-coated-hydrogels ↑cytotoxicity more than other hydrogel systems against LoVo cells	
SA, EGVE, HEA, PAP	Chemical (co-polymers grafting-based cross-linking)	MBA	CUR	Anticancer	• ↑solubility and drug loading • Maximum drug encapsulation efficiency (75%) • ↑drug release with sustained release behavior • ↓cell proliferation against MCF-7 and HepG2 cancer cells • ↓toxicity of carcinogenic cells in organs of Wistar rat models	[222]

6. Conclusion and future prospectives

The urge to develop smart systems with multifacet utility to improve the pharmaceutical and healthcare system has been the driving force in the technological advancement towards the development for novel materials and approaches for various biomedical applications. In this continued exploration, hydrogels have emerged as a persuasive candidate to be utilized as a carrier for drug/biomolecules and at the same time providing the ECM like behaviour enabling to mimic the 3D niche imitating a cellular environment. This far, the properties of alginate-based hydrogels have been extensively explored for numerous biomedical applications. However, the concentration of polymers and crosslinkers to develop the hydrogel interconnected network, the mesh size, porosity and degree of crosslinking are some parameters that has to be carefully monitored in order to achieve the clinical translations of these attractive delivery system.

In this review, the combination of curcumin and sodium alginate hydrogels have been extensively reviewed for cancer treatment and wound management. The selection of alginate as the base material of hydrogel formation and curcumin as a therapeutic molecule can not only be tagged as an effective approach both for cancer therapy and wound healing applications but is also cost effective that makes this a very attractive system. Apart from being a natural polymer with abundance occurrence, alginate hydrogel matrix has revealed long-time stability, cellular biocompatibility, and functionalization competence. On the other hand, curcumin has been shown to possess significant, anti-carcinogenic, anti-inflammatory, anti-oxidant, and anti-coagulant properties along with its utility in wound healing. In order to design a smart, multifunctional and effective curcumin loaded alginate hydrogel matrix for specific application, understanding the fate of these materials post cellular exposure is very

important. Hence, in this manuscript, the biological targets, cellular response and fate of curcumin inside the cells are comprehensively discussed. Both intrinsic and extrinsic parameters are carefully reviewed for their role in regulating the release behaviour of a drug from a hydrogel matrix.

However, alginate hydrogel matrix is mostly crosslinked with the help of chemical agents, which has to be completely removed before using these hydrogels for biomedical applications, Also, the degree of crosslinking in case of alginate hydrogels is a difficult parameter to be regulated. Further, the weak mechanical attributes are often associated with alginate matrix which can be modified with the help of different fillers like nanoparticles, addition polymers, crosslinkers etc. Another important aspect that is a hurdle in the clinical translation of alginate hydrogels is the lack of active cell binding sites on its surface. Doping of in case of alginate matrix with external molecules is another challenging task as the reaction parameters plays a very crucial role due to the degradation of alginate at high alkaline/acidic environment. Further challenges worthy of careful consideration are the sourcing of high-quality, reproducible alginate materials with controlled molecular structure, molecular weight and crosslinking efficiency. This will be critical as we move many of the above possibilities closer to clinical application and hence regulatory issues [225].

Additionally, the low aqueous solubility of curcumin is another task that needs to be confronted. Also, the condition in which curcumin is encapsulated in alginate matrix is very crucial in deciding the release behaviour of curcumin.

The shortcomings of alginate matrix can be addressed if instead of chemical crosslinkers, peptide linkers could be used for crosslinking as they can be cleaved by specific cells. Further, reduction in the crosslinking density could be another key factor that could be studied as a

function of mechanical attributes. Dual loading of curcumin along with other biomolecules/nanoparticles could be another approach to enhance the mechanical activity and prove a synergistic platform for multifunctional applications. An interdisciplinary approach could be utilized to make this system comprising of curcumin loaded alginate hydrogel matrix to be utilized in diverse biomedical applications.

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Conflict of Interest

The authors declare no conflict of interest.

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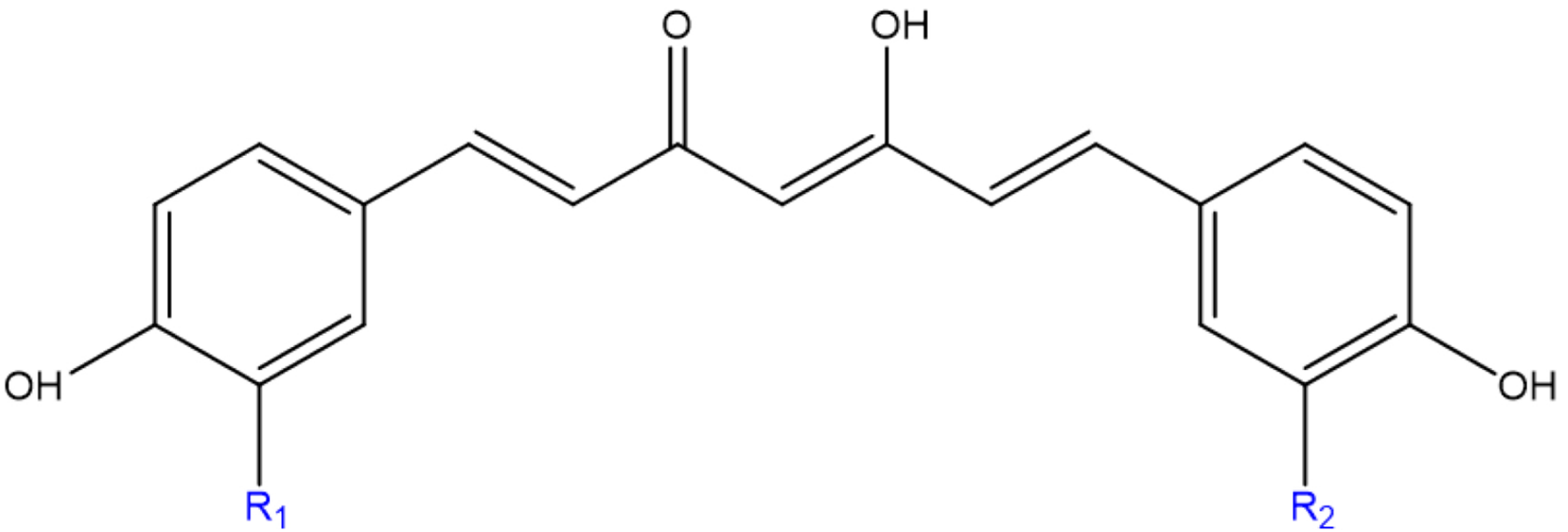
(a)



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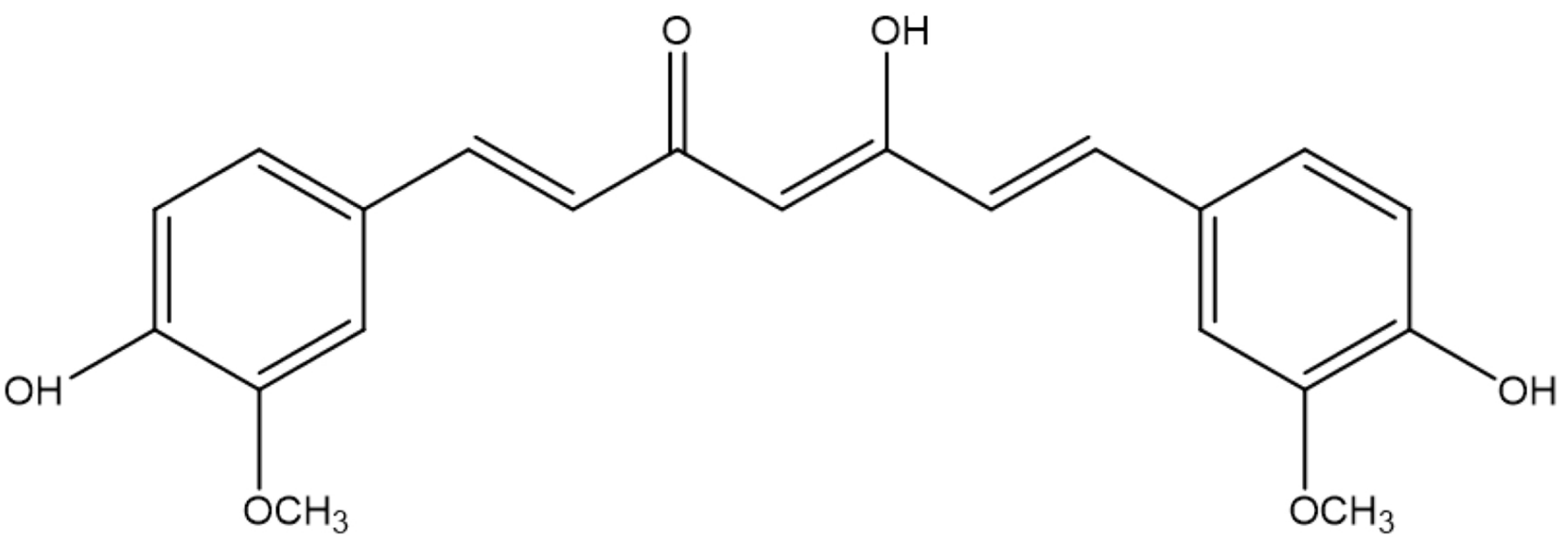


Figure 1

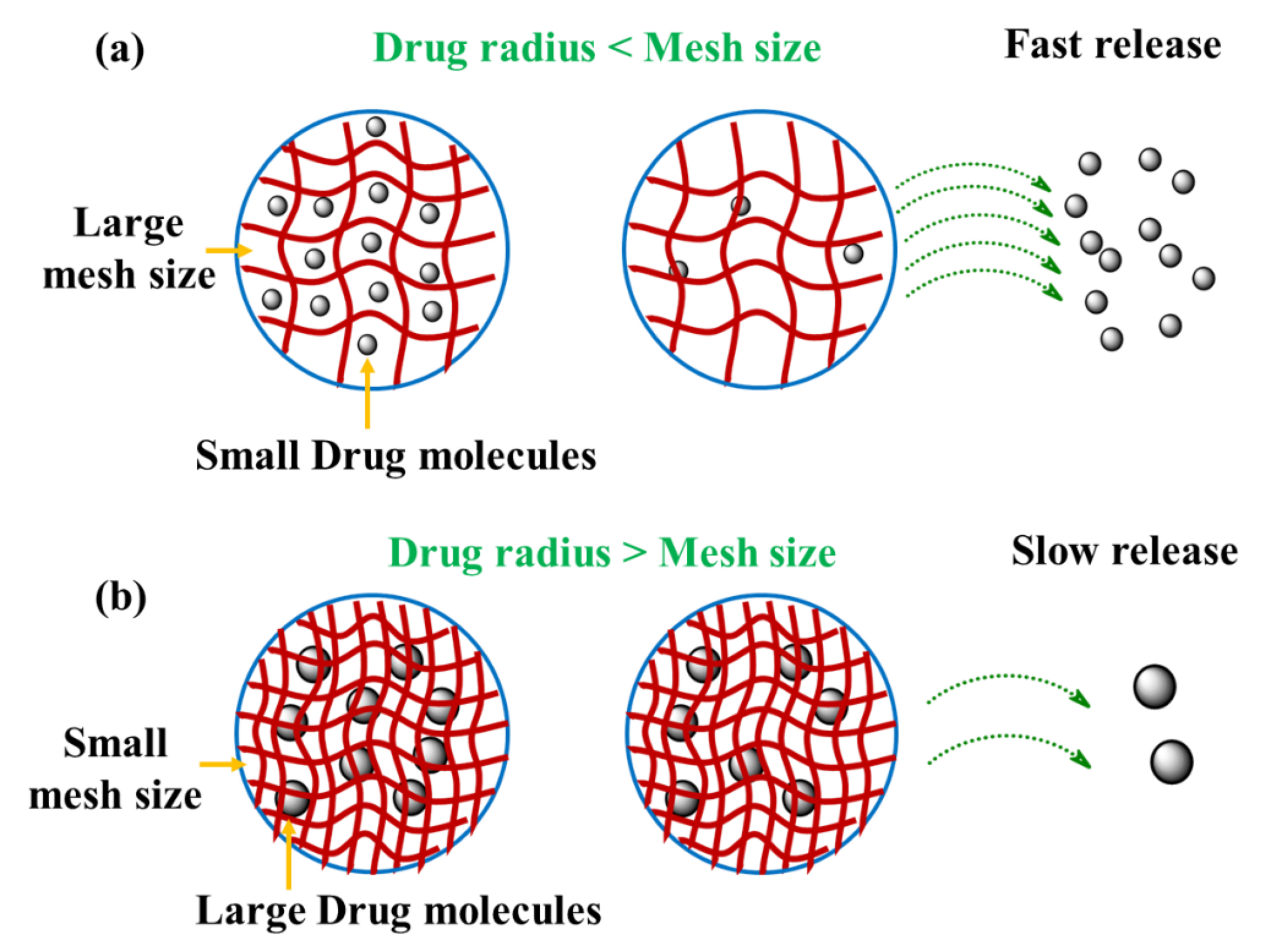

(a)
Drug radius < Mesh size
Fast release
Large
mesh size
Small Drug molecules
(b)
Drug radius > Mesh size
Slow release
Small
mesh size
Large Drug molecules

Figure 2

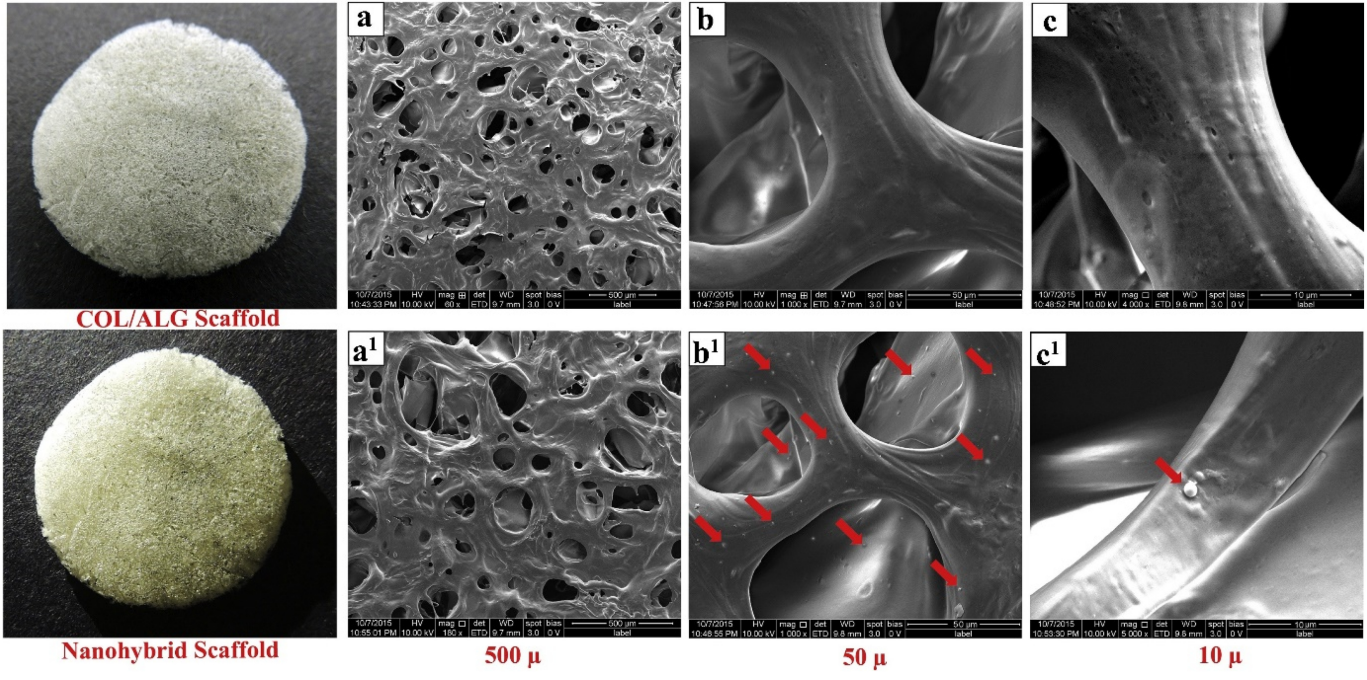

a
b
c
COL/ALG Scaffold
a1
b1
c1
Nanohybrid Scaffold
500 µ
50 µ
10 µ

Figure 3

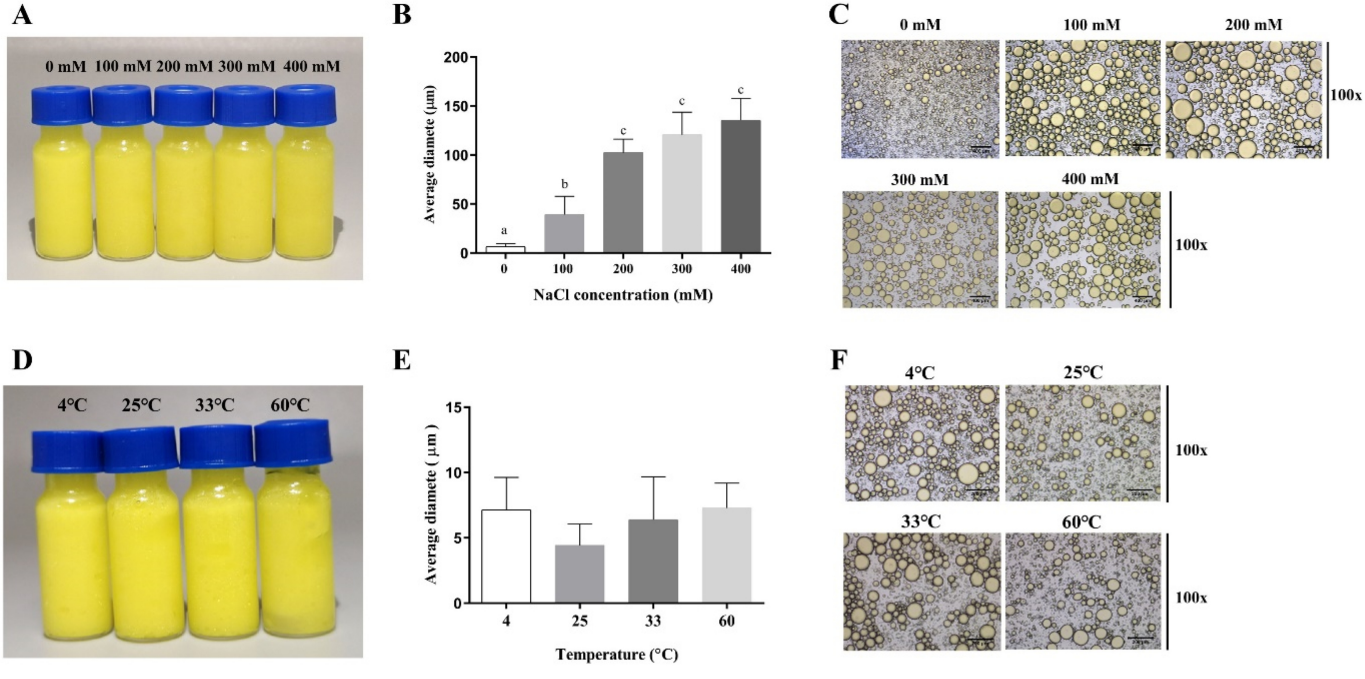

A
0 mM 100 mM 200 mM 300 mM 400 mM
B
Average diamete (μm)
200
150
100
50
0
a
b
c
c
c
0
100
200
300
400
NaCl concentration (mM)
C
0 mM
100 mM
200 mM
100x
300 mM
400 mM
100x
D
4°C 25°C 33°C 60°C
E
Average diamete (μm)
15
10
5
0
4
25
33
60
Temperature (°C)
F
4°C
25°C
100x
33°C
60°C
100x

Figure 4

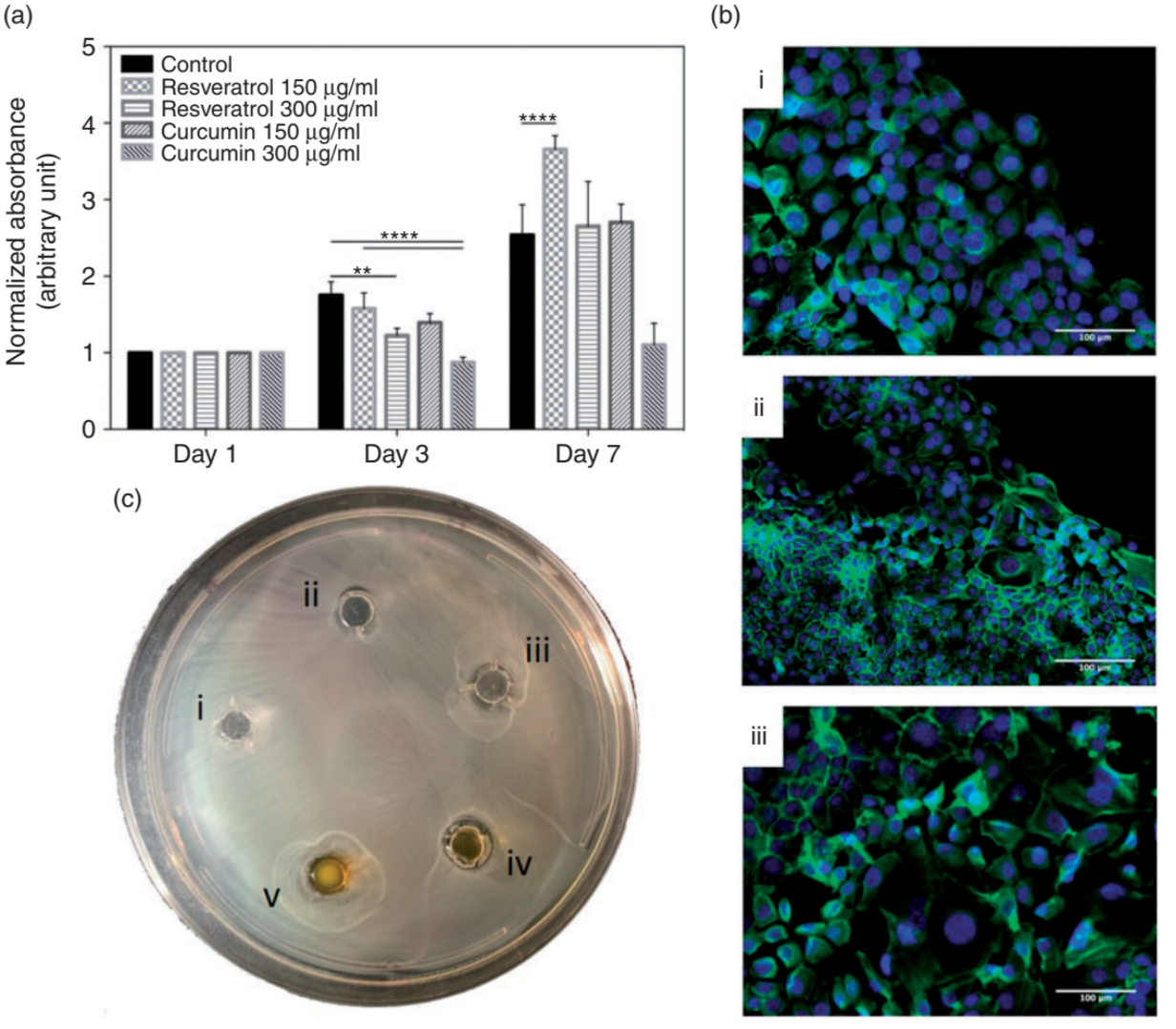
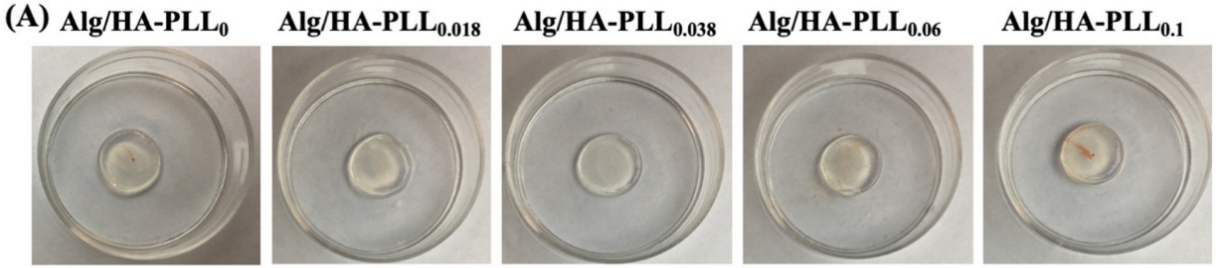
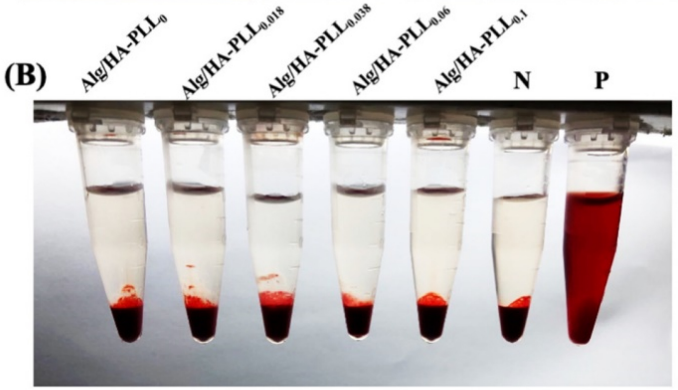

(a)
Normalized absorbance (arbitrary unit)
Control
Resveratrol 150 µg/ml
Resveratrol 300 µg/ml
Curcumin 150 µg/ml
Curcumin 300 µg/ml
****
****
**
Day 1
Day 3
Day 7
(b)
i
ii
iii
100 µm
(c)
i
ii
iii
iv
v

Figure 5


(A)
Alg/HA-PLL0
Alg/HA-PLL0.018
Alg/HA-PLL0.038
Alg/HA-PLL0.06
Alg/HA-PLL0.1


(B)
Alg/HA-PLL0
Alg/HA-PLL0.018
Alg/HA-PLL0.038
Alg/HA-PLL0.06
Alg/HA-PLL0.1
N
P

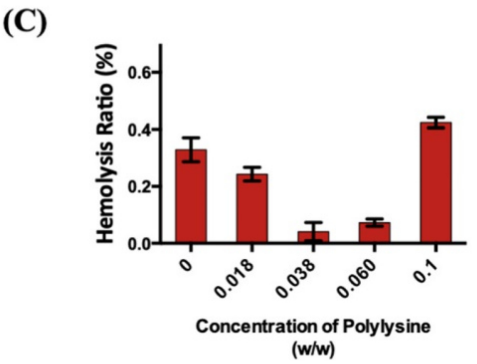

(C)
Hemolysis Ratio (%)
0.6
0.4
0.2
0.0
0
0.018
0.038
0.060
0.1
Concentration of Polylysine
(w/w)

Figure 6

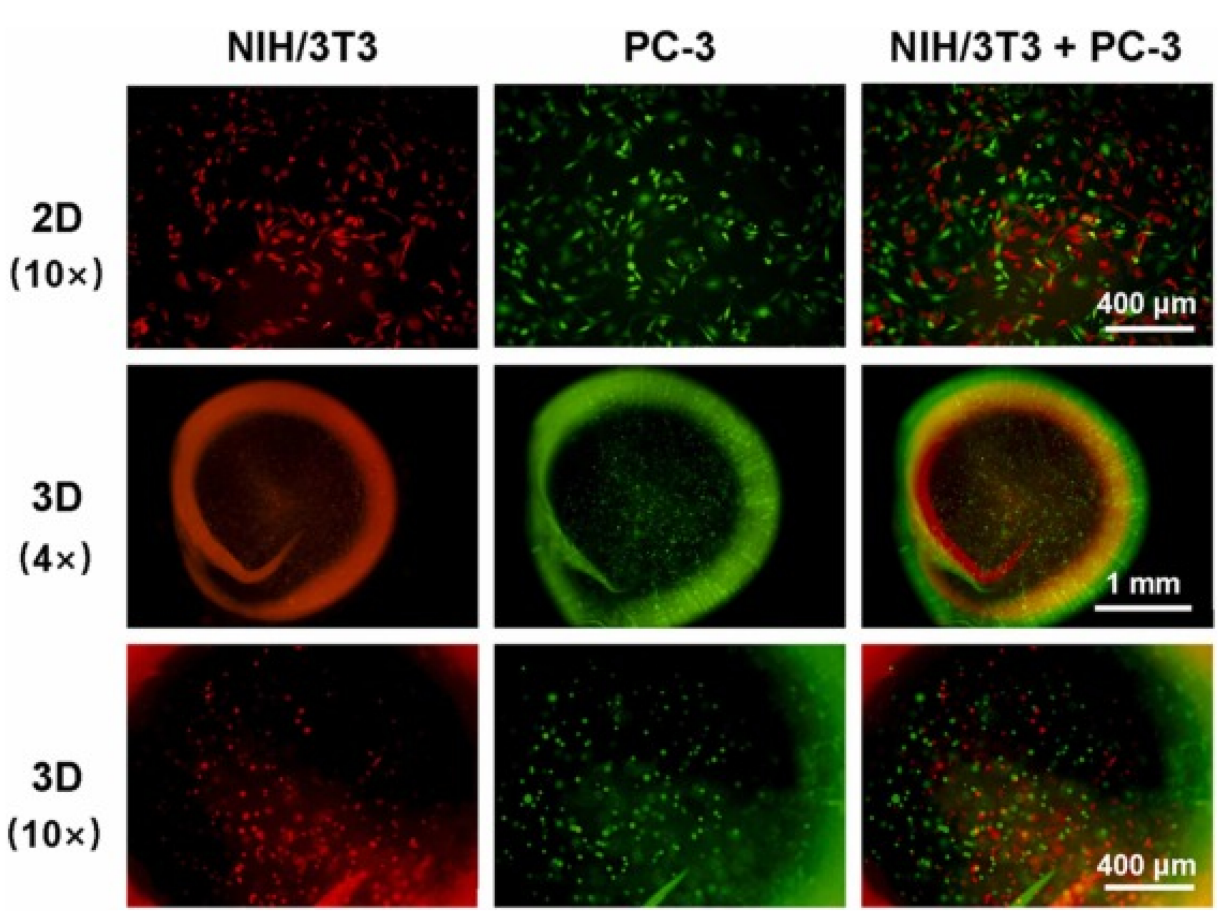


Figure 7

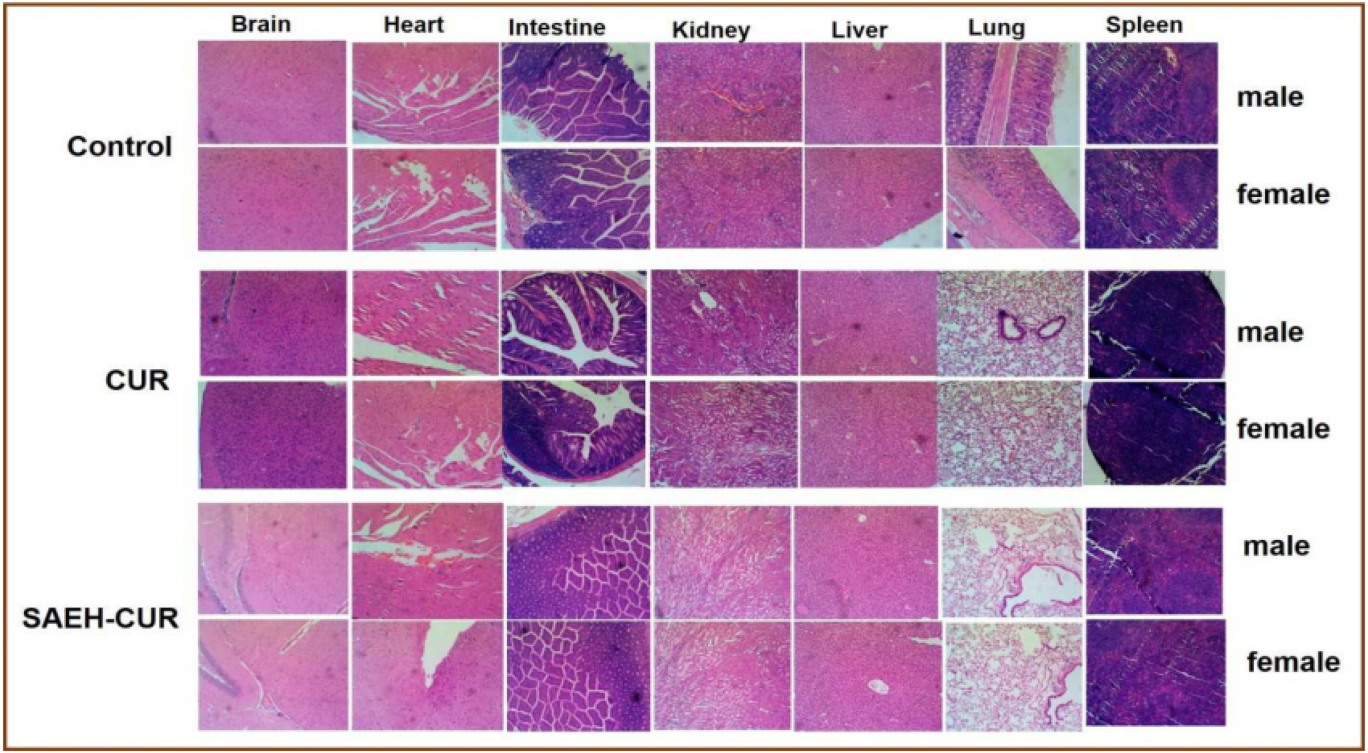

Brain
Heart
Intestine
Kidney
Liver
Lung
Spleen
Control
male
female
CUR
male
female
SAEH-CUR
male
female

Figure 8