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Review article

Arabinoxylans matrixes as a potential material for drug delivery systems development - A bibliometric analysis and literature review

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ABSTRACT

Arabinoxylans (AX) have become a focal point in the pharmaceutical sector owing to their physicochemical, biological, and functional properties. The purpose of this paper was to present a summary of the utilization of AX as drug release matrices through a bibliometric analysis (BA) and a literature review to spotlight the AX functional characteristics and their technological applications to promote this line of research. The BA was carried out using data from a Web of Science database research, specifically emphasizing the analysis of authors' keywords. This approach was chosen due to its significance in comprehensively understanding a particular research field and its relevance for in-depth knowledge of a research field. The BA outcomes revealed limited information concerning the AX applications in both release matrices and as excipients in the formulation and development of drug delivery systems (DDS), so there is a need for additional scientific and technological research in these areas to address the existing information gaps. However, the literature review shows that the native and modified AX from different delivery release systems, such as macrogels (including films, tablets, and hard gelatin capsules) and multi-particulate systems (including micro and nanogels), present an excellent potential as release matrices of biomolecules and drugs, such as doxorubicin, diclofenac sodium, caffeine, gentamicin, tizanidine hydrochloride, and insulin. In conclusion, AX have a wide potential for application in the pharmaceutical industry, so this work is expected to be a reference point for future research by scientists, technologists, and entrepreneurs who cope with the subject.

1. Introduction

In the past few years, there has been a notable surge in interest surrounding polymers obtained from renewable resources, marking them as a compelling and sustainable alternative. This growing enthusiasm is attributed mainly to the escalating concerns regarding

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Acronyms list

AA	acrylic acid
AC	ascending colon
ANN	artificial neural networks
AX	arabinoxylans
BCS	Biopharmaceutics Classification System
BSA	bovine serum albumin
BSG	brewers' spent grain
BSG-AX	arabinoxylan-rich fraction from brewers' spent grain
CCD	central composite design
CCRD	central composite rotatable design
CMAX	carboxymethyl arabinoxylan
CS	chitosan
CSLM	confocal scanning laser microscopy
DC	descending colon
DDS	drug delivery system
DM	dissolution medium
DOX	doxorubicin
DRDF	delayed-release dosage forms
DS	diclofenac sodium
DSC	differential scanning calorimetry
DT	dissolution testing
ERDF	extended-release dosage forms
*f*1	difference factor
*f*2	similarity factor
FA	ferulic acid
FAX	ferulated arabinoxylans
FT-IR	Fourier-transform infrared spectroscopy
GIT	gastrointestinal tract
GM	gentamicin
GO	graphene oxide
GX	glucuronoxylans
HM	heuristic method
IRDF	immediate-release dosage forms
MBAX	maize bran arabinoxylans
MDDS	multi-particulate drug delivery systems
Met-HCl	metformin hydrochloride
MH	metronidazole hydrochloride
MLR	multiple linear regression
MRDF	modified-release dosage forms
MRT	maximum release time
MWAX	maize wastewater arabinoxylans
N,N′-MBA	N,N′-methylene-bis-acrylamide
OERDF	oral extended-release dosage forms
PBS	phosphate-buffered saline
PAV	polyvinyl alcohol
PE	perindopril erbumine
PEG	polyethylene glycol
QSPR	quantitative-structure-property relationship
rGO	reduced graphene oxide
RS	rabeprazole sodium
S	stomach
SA	sodium alginate
SEM	scanning electron microscopy
SGJ	simulated gastric juice
SI	small intestine
SIF	simulated intestinal fluid
SPI	soy protein isolate
SS	silver-sulfadiazine

the exhaustion of fossil fuel reserves, environmental issues, particularly the release of greenhouse gases, and evolving government policies. In this context, renewable resources are derived from animal or plant species that can be used without compromising their survival and replenished through biological processes rather than the protracted timelines associated with geochemical processes [1]. In response to these challenges, contemporary development and research efforts in polymer-based drug delivery have shifted their focus towards harnessing the potential of polymers sourced from renewable origins. This strategic move addresses the imminent need for sustainable alternatives and aligns with the tenets of green chemistry and the circular economy. By emphasizing the utilization of renewable resources in drug delivery systems (DDS), scientists aim to contribute to a more sustainable future while reducing pharmaceutical practices' overall environmental impact [1–4].

Integrating natural excipients into DDS represents a pivotal advancement within the pharmaceutical landscape. These natural excipients, recognized for their inertness, safety, biocompatibility, and eco-friendliness [5], have been extensively explored in preceding studies, forming a cornerstone in pharmaceutical excipients [6–10]. The term "naturepolyceutics" has even been used to refer to natural polymers and drugs used to develop DDS [8].

DDS consists of a drug or a mixture of drugs associated with excipients, where the latter are pharmacologically inert materials [11,12]. DDS has two main categories: immediate-release (IRDF) and modified-release (MRDF) dosage formulations. MRDF can be additionally divided into delayed-release (DRDF) and extended-release (ERDF) dosage formulations [13]; the incorporation of modifiers of drug release achieves this [14].

Among the main advantages of using MRDF are improved patient compliance and adherence to treatment due to dosage reduction, achieving optimal concentration generally for long periods, elevated activity of labile drugs owing to its protection against harsh environments, coupled with diminished side effects resulting from reduced initial blood concentrations [7,15]. Furthermore, most clinically used small molecule drugs exhibit limited bioavailability and suboptimal pharmacokinetics attributed to their hydrophobic nature and low molecular mass, so polymer-based MRDFs may enhance the effectiveness of these drugs by improving their water solubility, extending their circulation time, increasing the deposition of the drug in the target tissue, and reducing the risk to normal tissues [16].

Arabinoxylans (AX) constitute non-starch polysaccharides and represent one of the most prevalent polysaccharides found in the cell walls of cereal grains. Nevertheless, they are also found in various lignocellulosic materials, including plant biomass from different agri-food processes. Their presence in diverse sources underscores their versatility and highlights several distinctive characteristics that render them suited for applications in DDS [17]. Firstly, the ability of ferulated arabinoxylans (FAX) to form hydrogels, makes them valuable as matrices for the controlled release of bioactive compounds [18]. These hydrogels can be utilized to encapsulate and deliver drugs in a sustained manner, enhancing their bioavailability and therapeutic efficacy.

Additionally, AX have been shown to possess immunomodulatory properties, which can be beneficial for targeted drug delivery and modulation of immune responses in the context of certain diseases, like cancer [19,20]. Moreover, the biocompatibility and biodegradability of AX make them suitable for use in DDS, ensuring minimal adverse effects and promoting environmentally friendly pharmaceutical formulations [21,22]. The rheological properties of AX also contribute to their relevance in drug delivery since they can be used to fabricate hydrogels and films for various pharmaceutical applications, including controlled-release formulations and mucoadhesive oral films [23,24]. Overall, the unique properties of AX, such as their gelling behavior, immunomodulatory effects, biocompatibility, and rheological characteristics, position them as promising materials for the development of advanced DDS.

On the other hand, integrating materials derived from agri-food by-products into the circular economy is paramount for sustainable resource management and waste reduction. By utilizing AX extracted from agri-food by-products, such as maize bran, wheat bran, and brewers' spent grain, researchers can contribute to the valorization of these by-products, thereby reducing waste and encouraging the effective utilization of agricultural resources [25–27]. On the other hand, AX utilization in the development of functional materials, such as films, coatings, and hydrogels, aligns with the principles of the circular economy through the promotion of the reusability and recyclability of agro-food by-products [17,18,27–29]. Thus, by exploring the AX uses in drug delivery, researchers can contribute to developing sustainable pharmaceutical formulations that minimize environmental impact and promote the circular use of natural

SSIM	simulated small intestinal medium
TAX	thiolated arabinoxylan
TAX-co-AA	thiolated arabinoxylan/acrylic acid hydrogels
TC	transverse colon
TEOS	tetraethyl orthosilicate
TGA	thioglycolic acid
TZN-HCl	tizanidine hydrochloride
UFS	unsupervised forward selection
UDDS	unit dose distribution systems
USP-PDA-II	United States Pharmacopeia (USP) dissolution apparatus 2 (paddle apparatus)
WEAX	water-extractable arabinoxylans
WoS	Web of Science©
WUAX	water unextractable arabinoxylans
WUAX-SPI	water-unextractable arabinoxylans-soy protein isolate
α-L-Ara*f*	α-L-arabinofuranosyl units
β-D-Xyl*p*	β-D-xylopyranoside units

resources.

Finally, utilizing a bibliometric approach to analyze and synthesize the existing literature on AX applications in DDS development and related topics is essential for several reasons. Firstly, a bibliometric analysis provides a quantitative and systematic method for evaluating the existing body of literature, enabling researchers to identify the most impactful publications, authors, and research trends within a specific field [30,31]. This approach allows for the comprehensive mapping of research landscapes, identifying emerging topics, research gaps, and the evolution of knowledge over time [32,33]. This approach enables researchers to gain comprehensive insights into research landscapes, identify emerging trends, and contribute to evidence-based decision-making, advancing knowledge and promoting sustainable practices within the agri-food and pharmaceutic sectors [34,35].

Based on all of the above, the objective of this publication was to present an overview of the literature on the use of AX as release matrices of bioactive compounds and active principles through a bibliometric analysis based on the results obtained through a search on the Web of Science (WoS) database and a literature review, to highlight its functional properties, its technological applications, and its feasibility when developing DDS, in addition to promoting this line of research, being a viable alternative for the integration of agri-food by-products within a circular economy.

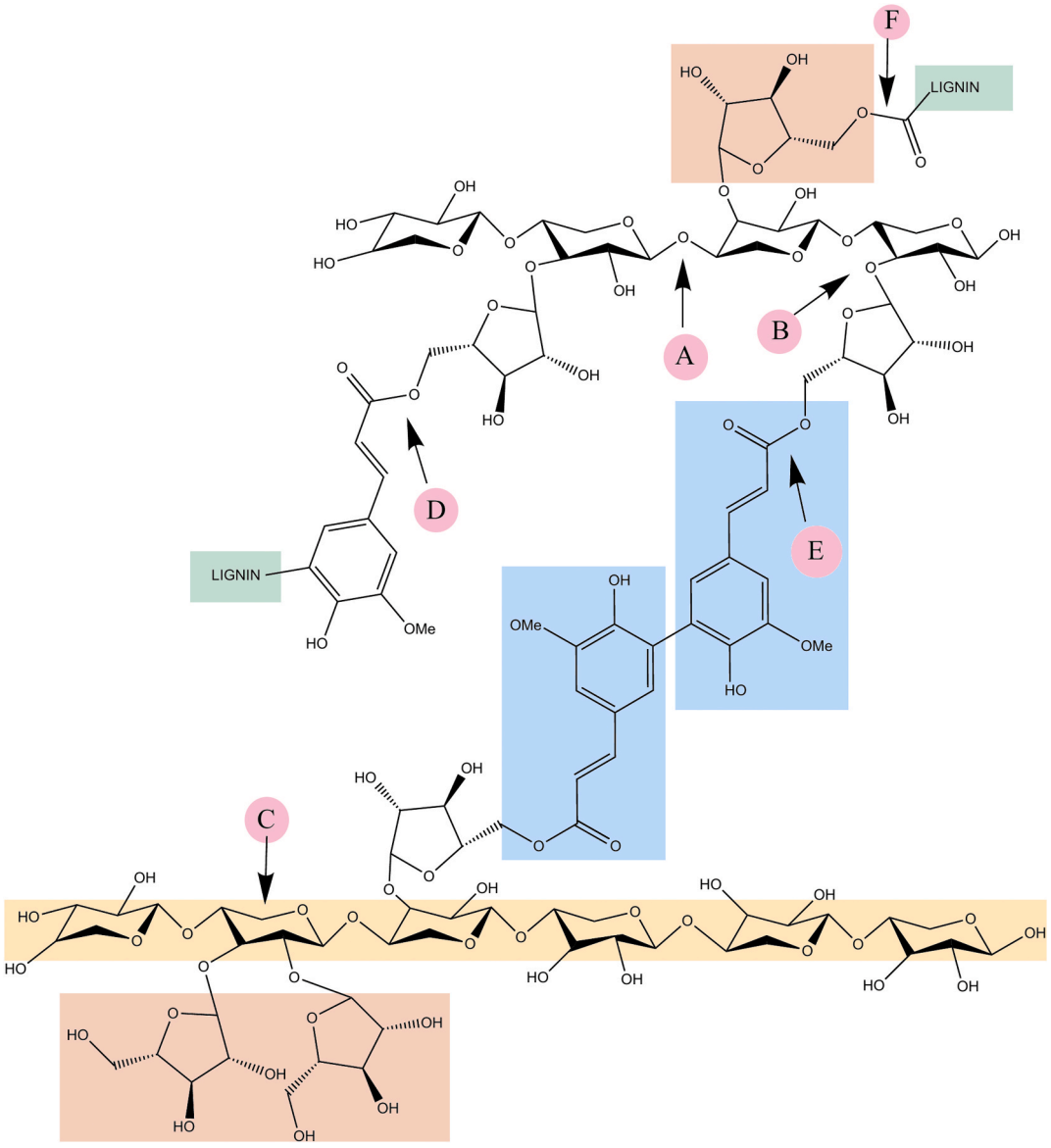
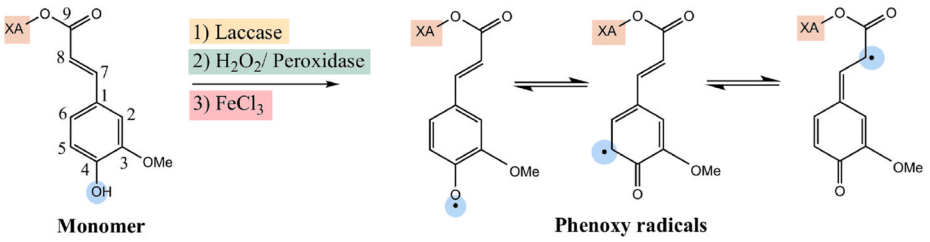
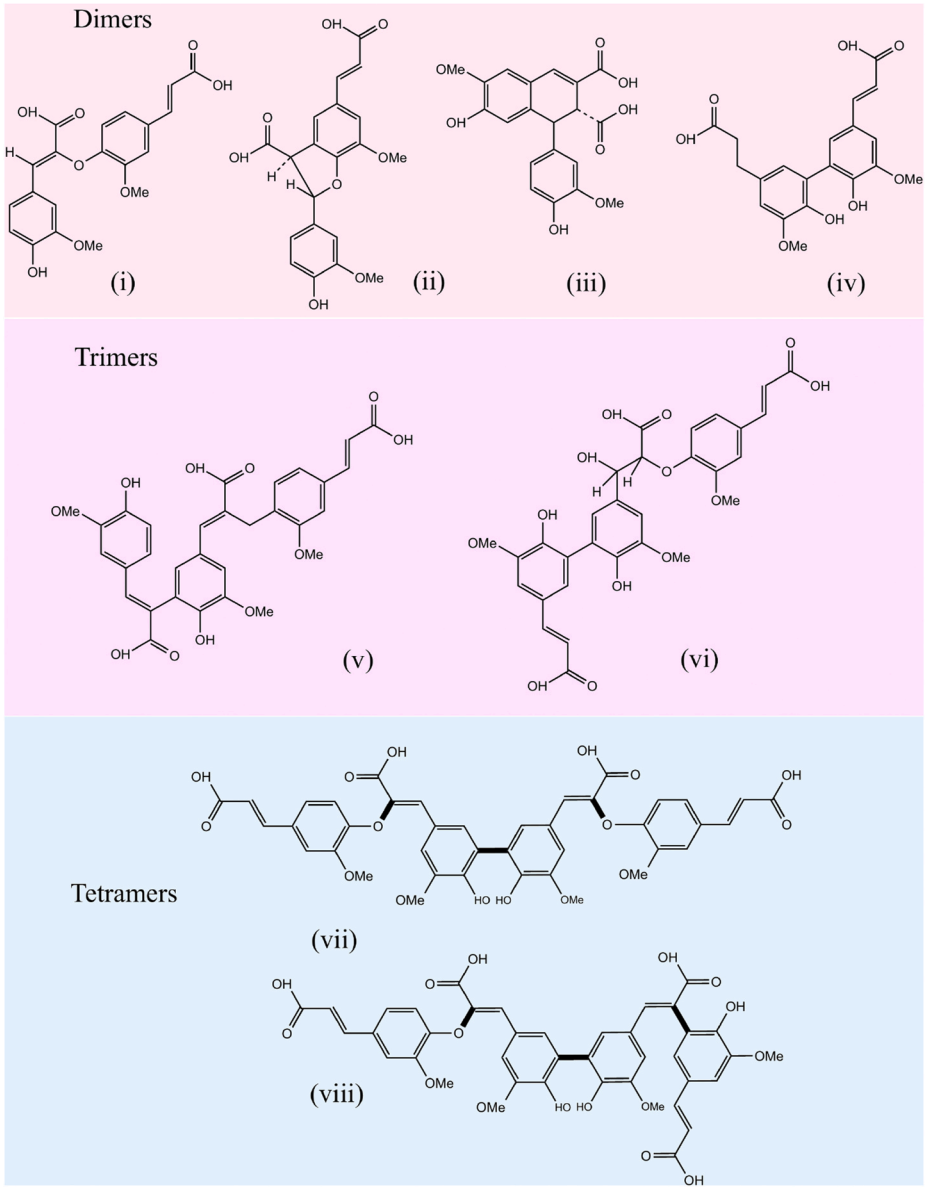


Fig. 1. Generalized structure of arabinoxylans. **A:** β-(1 → 4) linked β-D-Xyl*p* backbone, **B:** β-D-Xyl*p*-α-L-Ara*f* linkage, **C:** disubstituted β-D-Xyl*p* residue, **D:** 5-*O*-feruloyl lignin, **E:** 5-*O*-diferuloyl group (5-5′ linked dimer), and **F:** α-L-Ara*f*-lignin.



(a)



(b)

(caption on next page)

Fig. 2. Gelling mechanism. (a) The chemical or enzymatic agent induces the oxidation of FA, forming dimers, trimers, and oligomers via a radical mechanism in which the AX chains are linked with covalent bonds. (b) Chemical structure of some FA dimers, trimers, and tetramers. Some of the commonly occurring ferulate dehydrodimers identified in grasses: (i) 8-*O*-4 dimer, (ii) 8-5 dimer, (iii) 8-8 dimer, and (iv) 5-5 dimer [59]. Trimers and tetramers extracted from insoluble maize bran fiber: (v) 8-*O*-4/8–5 (non-cyclic) dehydrotriferulic acid, (vi) 5-5/8-*O*-4(H_2O)-dehydrotriferulic acid; (vii) 4-*O*-8/5-5/8-*O*-4-dehydrotetraferulic acid and (viii) 4-*O*-8/5-5/8-5 (noncyclic)-dehydrotetraferulic acid.

2. Arabinoxylans

AX are composed of a backbone made up of units of β-D-xylopyranoside (β-D-Xyl*p*) linked by β-(1 → 4) glycosidic bonds, at which α-L-arabinofuranosyl groups (α-L-Ara*f*) are linked by α-(1 → 3) and/or α-(1 → 2) bonds [27,36] (Fig. 1). AX can be substituted in different positions with other sugars like glucose, mannose, galactose, etc., and can also have acetyl groups and uronic acids, exemplified by glucuronic acid [18,37–40]. According to their extractability, which depends on their solubility in water, they can be categorized as water-extractable arabinoxylans (WEAX) and water-unextractable arabinoxylans (WUAX) [41]. WEAX are loosely bound to the cell wall surface, while WUAX are linked to other components of the cell wall matrix, such as proteins, lignin, or lignans, through hydrogen and covalent bonds [42].

One distinctive structural attribute in AX is the presence of hydroxycinnamic acids. Some residues of α-L-Ara*f* are linked by ester bonds at positions *O*-5 to hydroxycinnamic acid subunits (HCA), such as 3-methoxy-4-hydroxycinnamic acid or ferulic acid (FA) and 4-hydroxycinnamic acid or *p*-coumaric acid (p-CA) [43,44], being the FA the most reported in AX. The AX with FA in their chemical structure are called feruloylated arabinoxylans (FAX) [45]. Fig. 1 shows the chemical structure of FA bound to a molecule of α-L-Ara*f*. The amount of FA linked to the AX molecule is small, ranging from 0.2 to 0.4 % in the case of WEAX and 0.6–0.9 % for WUAX. That shows that for 1000 residues of β-D-Xyl*p*, there are from 2 to 4 and from 6 to 9 FA units, respectively [39].

The FA content influences the physicochemical properties of the AX since the coupling of at least two FA residues through a covalent bond produces the cross-linking of the AX chains, leading to increased viscosity of the solution and triggering the formation of hydrogels [46,47] (Fig. 2). These crosslinks are produced through the phenoxy radical-mediated oxidative polymerization of FA units [48] after oxidation of the FA molecule by chemical agents ($FeCl_3$ or $(NH_4)_2S_2O_8$) or enzymes (peroxidase/H_2O_2, laccase/O_2, and linoleic acid/lipoxygenase) [18,49–51] (Fig. 2a). These covalent crosslinks result from the formation of upper FA structures. FA monomers, dimers, trimers, and tetramers have been recognized in AX chains [45,52–54]; some of these structures are shown in Fig. 2b. The most common FA dehydrodimers or dehydrodiferulic acid (di-FA) molecules are those with the bonds 5-5′, 8–5′, 8-*O*-4′, 4-*O*-5′, 5–8′, 8-8′, being preponderant forms 8-8′, 8–5′ and 8-*O*-4′ [39,55–60]. On the other hand, it has also been mentioned that FA can establish covalent bonds with different molecules, such as proteins or lignin [48,61]. These hydrogels possess significant water-holding capabilities, rendering them potent encapsulation matrices with diverse pharmaceutical, cosmetic, and food applications [18,62–64].

AX can be extracted from different lignocellulosic materials, such as the endosperm, the aleurone layer, and the pericarp of cereals [39,65,66], bamboo shavings [67], banana peels [68], sugarcane bagasse [69], and carrot pomace [70], among others. Previously, different extraction methods of AX have been reviewed [37,38,66]. AX have been extracted with water and chemical, enzymatic, and physical agents [66].

Extraction yield, molar mass (Mw), pattern, and degree of substitution with α-L-Ara*f* units, as well as the FA content and the solubility, among others, are characteristics that depend on the method and the extraction source used, and that will determine the chemical structure, the physicochemical properties, and the functionality of the AX [18,39], and therefore, its technological applications. For example, the extraction method should not cause degradation of hemicelluloses, as a molecular mass exceeding 5 kDa is essential for producing high-value items like barrier films or hydrogels [71]. In general, research on the ability of hemicelluloses to form hydrogels and films has been extensive, mainly because they show biocompatibility and biodegradability properties [72]. These features are important for drug delivery, cell therapy, emulsification, and encapsulation [73–76]. In addition, non-starch polysaccharides, such as AX, resist the digestive action of gastrointestinal enzymes and maintain their integrity in the upper gastrointestinal tract. However, upon reaching the colon, bacterial polysaccharidases initiate their degradation, indicating their potential application in the design of specific release matrices [6,9,18]. The native and modified AX present satisfactory physicochemical properties as pharmaceutical excipients [10,74,77].

AX have been modified by blending with other polymers, and chemical and enzymatic modifications have been made to customize their properties and give them specific applications [48,73,78–80]. Polysaccharides such as AX have been modified to improve solubility, mechanical properties, biodegradability control, add hydrophobicity, conformation, and manufacturing [81]. In the case of AX, esterification has been reported [82], succinylation [83], carboxymethylation [84,85], thiolation [86], and the ethylation [87] of AX, as well as its copolymerization with other materials such as acrylic acid (AA) [88], polyethylene glycol (PEG) [89] and its functionalization with Na [77]. This to modify its properties for its application in pharmaceutical products, cosmetics, food additives, composites, etc [82,87,90]. For example, the union of AX with PEG has been used to add plasticity to the polymer and form foams for prospective applications in the pharmaceutical industry in the development of drug delivery systems (DDS) [89].

The toxicity of AX has also been studied. For example, in three animal species, the acute toxicity of an excipient made from AX isolated from the shell of Ispaghula (*Plantago ovata*) showed that acute administration of AX could be safe [91]. It has also been reported that xyloglucan, another group of hemicelluloses, is not toxic, does not irritate ocular tissues, and is not hemolytic [92].

Table 1
Drugs and bioactive compounds in vitro release studies using macroscopic AX hydrogels.

Delivery system	Molecule tested	Release conditions	Final release percentage (%, w/v)	Reference
WEAX gels at 1 % (w/v) in AX with different FA contents (μg/mg AX): 2.3 (gel 1), 1.8 (gel 2), 1.6 (gel 3), and WEAX gels at 1 (gel 4), 1.5 (gel 5), and 2 % (w/v) (gel 6) in AX and same initial FA content (2.3 μg/mg AX), all gels reticulated with laccase (1.675 nkat/mg AX)	Bovine serum albumin	Dissolution testing (DT): 25 °C and 90 rpm tangential rotation Dissolution medium (DM): Sodium azide (0.02 %, w/v) Maximum release time (MRT): 24 h	≈73 (from gel 1) ≈78 (from gel 2) ≈90 (from gel 3) ≈70 (from gel 4) ≈65 (from gel 5) ≈50 (from gel 6)	[56]
Gels at Ovalbumin/WEAX mass ratios (MR) of 1, 2.5, 5, 7.5, and 10 reticulated with laccase (1.675 nkat/mg AX) Ovalbumin/WEAX mixtures (Ov/AX mass ratios (MR): 1, 2.5, 5, 7.5, 10) reticulated with laccase (1.675 nkat/mg AX)	Ovalbumin	DT: 25 °C and 90 rpm tangential rotation DM: Sodium azide (0.02 %, w/v) MRT: 24 h	70 ± 1 (for MR: 1) 75 ± 1 (for MR: 2.50) 82 ± 1 (for MR: 5) 86 ± 2 (for MR: 7.50) 88 ± 1 (for MR: 10)	[55]
Gel 1: 2.50 % (w/v) WUAX reticulated with laccase (2 U/mg AX) Gel 2: 3.50 % (w/v) WUAX reticulated with laccase (2 U/mg AX)	Insulin	DT: 25 °C and 90 rpm tangential rotation DM: Sodium azide (0.02 %, w/v) MRT: 15 h	16 ± 2 (from gel 1) 14 ± 1 (from gel 2)	[104]
2.50 % (w/v) WUAX reticulated with laccase (1.675 nkat/mg AX)	Insulin (for test 1) and *β*-lactoglobulin (for test 2)	DT: 25 °C and 90 rpm tangential rotation DM: Sodium azide (0.02 %, w/v) MRT: 15 h	18 ± 1 (insulin) 11 ± 1 (β-lactoglobulin)	[103]
2 % (w/v) WUAX reticulated with peroxidase (88 μg/mg AX)	Caffeine	DT: United States Pharmacopeia (USP) dissolution apparatus 2 (paddle apparatus) (USP-PDA-II) at 37 ± 0.50 °C and 50 rpm DM: distilled water and 0.1 mol/L HCl MRT: 3 h	7 (in water) 10 (in 0.1 mol/L HCl)	[105]
Gel 1: 3 % (w/v) WUAX reticulated with laccase (1.675 nkat/mg AX) Gel 2: 4 % (w/v) WUAX reticulated with laccase (1.675 nkat/mg AX) In both cases with triton X-100 placed on the gel surface	Lycopene (with 12.50 mg in gel 1 and 16.0 mg in gel 2)	DT: 25 °C and 90 rpm tangential rotation DM: Sodium azide (0.02 %, w/v) with sodium taurocholate MRT: 4 h	3.70 ± 0.20 (from gel 1) 2.60 ± 0.30 (from gel 2)	[24]
Gels with standard proteins/WUAX mass ratios of 0.06 and 0.12 reticulated with laccase (1.675 nkat/mg AX)	Insulin (for test 1), ovalbumin (for test 2), and bovine serum albumin (for test 3)	DT: 25 °C and 90 rpm tangential rotation DM: Sodium azide (0.02 %, w/v) MRT: 8 h	6.20 ± 0.40 (insulin at 0.06 protein/WUAX MR) 7.50 ± 0.50 (insulin at 0.12 protein/WUAX MR) 5.10 ± 0.50 (ovalbumin at 0.06 protein/WUAX MR) 4.40 ± 0.30 (ovalbumin at 0.12 protein/WUAX MR) 3.50 ± 0.20 (ovalbumin at 0.06 protein/WUAX MR) 3.20 ± 0.30 (ovalbumin at 0.12 protein/WUAX MR)	[102]
WUAX emulsion (formulation 1), soy protein isolate (SPI) (formulation 2), WUAX (formulation 3), and WUAX-SPI (formulation 4) emulsion-filled gels.	*β*-carotene	DT: 37 °C and 100 rpm tangential rotation DM: simulated gastric juice (SGJ) and simulated small intestinal medium (SSIM) MRT: 2 h in SGJ and 6 h in SSIM	≈76 (from formulation 1) ≈68 (from formulation 2) ≈42 (from formulation 3) ≈38 (from formulation 4)	[106]
Three gels of carboxymethyl arabinoxylan (CMAX) co-polymerized with acrylic acid (AA) and reticulated with N,N′-methylene-bis-acrylamide (N,N′-MBA) varying CMAX concentration: 1 (gel 1), 1.50 (gel 2), and 2 % (gel 3) (w/w)	Rabeprazole Sodium	DT: Use of USP-PDA-II at 37 ± 0.50 °C and 100 rpm DM: 0.60 mol/L Tris Buffer (pH 8) MRT: 24 h	92.83 (from gel 1) 96.76 (from gel 2) 98.44 (from gel 3)	[88]

(*continued on next page*)

Table 1 (*continued*)

Delivery system	Molecule tested	Release conditions	Final release percentage (%, w/v)	Reference
TAX-co-AA hydrogels reticulated with N,N′-MBA: Formulation TAX1: 2.50 % TAX and 25 mL of AA Formulation TAX2: 2 % TAX and 25 mL of AA	Perindopril erbumine	DT: Use of USP-PDA-II at 37 °C and 100 rpm DM: phosphate buffer (pH = 7.4) MRT: 24 h	≈82 (from TAX1) ≈83 (from TAX2)	[86]

3. Drugs and bioactive compounds in vitro release studies using arabinoxylan hydrogels

Hydrogels are polymeric networks with hydrophilic properties created through the physical or chemical cross-linking of gelator molecules under optimal conditions. The cross-linking agent type and the cross-linking degree influence the mesh size. Physically cross-linked hydrogels result from non-covalent interactions among polymers, including van der Waals/electrostatic/dipole-dipole forces, hydrogen bonding, π-π stacking, or entanglements within the polymeric networks. This is in contrast to chemically cross-linked hydrogels, which feature stable covalent bonding between polymer chains and consequently exhibit enhanced mechanical strength [93]. The widespread appeal of hydrogels can be ascribed to four key properties: biodegradability, biocompatibility, drug-loading capacity, and controlled drug release [94].

In the context of drug administration, diverse sizes and structures dictate the distinct functions of hydrogels and the delivery routes through which they are applied. For instance, hydrogels can be categorized into three groups based on their size [94–96]:

I. macroscopic gels, including coatings and films with delivery routes: in situ injection, in situ implantation, and transdermal delivery (transdermal patch) (>100 μm), although in this review, some AX-based multiparticulate systems with sizes larger than 100 μm were also considered;
II. microgels (100 nm - 100 μm) with delivery routes: oral delivery, pulmonary delivery, and transarterial chemoembolization; and
III. nanogels (<100 nm) with intravenous and in situ delivery routes.

The process of drug release from hydrogels consists of different stages: hydrogels absorb water upon contact with biological fluids, undergo swelling, and release the encapsulated drug through diverse phenomena and mechanisms that include dissolution/diffusion, osmotically driven release, and erosion, or a combination of the previous [97]. The in vitro release mechanisms can be interpreted, fitting the experimental data of the release of the drug with the models of Fick, Weibull, Higuchi, Korsmeyer-Peppas, Baker and Lonsdale, Hopfenberg, Corrigan, Hixson-Crowell, Sivak, and Kopcha [97,98]. In the process of dissolution, the performance of the polymer system is pivotal and is influenced by various factors, including drug properties, formulation, release medium, and others [15, 97].

3.1. Macroscopic hydrogels

AX has a great water-holding capacity, reaching up to 100 g of water per gram of dry cross-linked polymer [99]. The water-holding capacity of AX is higher than protein and starch, about five to ten times [100].

An investigation proposed a strategy to produce more concentrated and less brittle hydrogels, using osmotic compression to extract water, reinforcing the mechanical resistance. Notably, the compression also resulted in a slight enhancement in gel connectivity, presumably by creating additional cross-links upon compression. The swollen gels exhibit a uniform structure with mesh sizes of approximately 200 nm, rendering them suitable for encapsulation purposes [62]. A limited swelling capacity implies a gradual drug release, suggesting that the polysaccharide could be employed as a polymer for controlled-release formulations [101]. Covalently bonded AX hydrogels exhibit resistance to pH changes, ensuring that their swelling behavior remains unaffected by ionic charges; nevertheless, they are fermented by colonic microbiota [18].

Previous studies have shown that AX hydrogels can be used as controlled delivery vehicles for active ingredients, as shown in Table 1, due to their macroporous structure with mesh sizes ranging from 40 to 400 nm [57]. Experiments have been performed on protein [55,56,102–104], lycopene [24], and caffeine [105] release. In this last work, caffeine release experiments were conducted in both distilled water and 0.1 mol/L HCl, providing a comparison with the conditions of gastrointestinal fluid, using the United States Pharmacopeia (USP) dissolution apparatus 2 (paddle apparatus) (USP-PDA-II).

It has been shown that the FA concentration in the AX molecule and the AX concentration in the hydrogel directly influence the bovine serum albumin (BSA) release rate from WEAX hydrogels. The release rate increased when the initial FA content in the hydrogels decreased from 2.3 to 1.6 μg/mg AX, while the release rate decreased as the concentration of WEAX in the hydrogel increased (from 0.5 to 2 %, w/v) [56]. The result can be attributed to more cross-links between AX chains in both cases. A higher content of FA contributes to a greater formation of cross-links and increases the concentration of AX, which decreases the rate of BSA release and produces the effect of sustained release.

In other research, applying WUAX in emulsion-filled gels was evaluated as an efficient method to augment the protective and controlled release characteristics of β-carotene. Water-unextractable arabinoxylans-soy protein isolate (WUAX-SPI) emulsion-filled

gels were created by incorporating a WUAX emulsion containing 10 mL/100 mL soybean oil in a dispersion of WUAX and SPI polymer followed by gelation. The release kinetics of β-carotene in different incorporated systems were investigated during in vitro simulated digestion. The findings revealed that the WUAX-SPI emulsion-filled gels exhibited superior sustained release performance compared to both WUAX and SPI emulsion-filled gels. Consequently, the gel demonstrated higher strength and stability, providing better protection for β-carotene [106].

Regarding the chemical modifications of AX, the synthesis of carboxymethyl arabinoxylan (CMAX) has previously been reported, which was copolymerized with acrylic acid (AA), and N,N′-methylene-bis-acrylamide (N,N′-MBA) was used as crosslinker, to obtain a polymeric network sensitive to pH (CMAX-g-AA) for the controlled release of rabeprazole sodium (RS). Different formulations of hydrogels were evaluated, varying AA, CMAX, and N,N′-MBA concentrations. With the escalation of CMAX concentration, the swelling of hydrogels demonstrated a direct proportionality to drug release (92.83 %, 96.76 %, and 98.44 % at CMAX concentrations of 1 %, 1.5 %, and 2 %, respectively at basic pH). Conversely, the augmentation of N,N′-MBA concentration led to an overall reduction in swelling, attributed to the increasing crosslinking density of the polymer chain, consequently resulting in a decrease in drug release. Results revealed highly pH-sensitive swelling, resulting in drug release at intestinal pH [88]. In this investigation, an in vivo evaluation was also carried out. Before, it is necessary to mention that C_{max} is a standard measurement in pharmacokinetics, referring to the peak serum concentration of a drug after administered and before the second dose [88]. The formulations displaying the maximum cumulative in vitro drug release were chosen for in vivo assessment. In vivo evaluation in rabbits of both genders indicated an enhancement in relative RS bioavailability by demonstrating an increase in the C_{max} of the RS using the polymeric carrier network (CMAX-g-AA) versus the same oral dose of RS drug solution, showing significantly different C_{max} with values of 103.71 $\pm$ 16.081 and 61.263 $\pm$ 5.37 ng/mL, respectively.

Likewise, the esterification of AX with thioglycolic acid has been reported to synthesize thiolated arabinoxylan (TAX), which was copolymerized with AA to prepare hydrogels using N,N′-MBA as a crosslinking agent. These pH-dependent thiolated arabinoxylan/acrylic acid hydrogels (TAX-co-AA) were prepared from different formulations with different concentrations of TAX, AA, and N,N′-MBA, and their impact on solvent penetration, swelling, and subsequent drug release was examined. Perindopril erbumine (PE) was used as a model drug [86]. Dissolution studies were performed at pH 1.2 and 7.4, where drug release directly correlated with the TAX and AA ratio. A barrier in PE release was the thickness of the hydrogel. As the hydrogel thickness increased with greater swelling, there was a corresponding decrease in drug release. In essence, controlling TAX concentration enables the regulation of hydrogel thickness, subsequently influencing drug release. Besides, an increment in the swelling index was noticed when increasing the AA content in the hydrogel formulation because of its ionizable -COO^- group in the alkaline media. However, in the acidic media, deprotonation of this group resulted in the collapse of the hydrogel network. PE release studies showed drug release increased in the alkaline medium as the swelling index increased. The hydrogel formulation, containing 2.5 % TAX and 25 mL AA (TAX1), demonstrated a noteworthy escalation in swelling, followed by drug release, compared to a formulation containing 2 % TAX and 25 mL AA (TAX2). This research also conducted an in-vivo study of PE by administering an oral drug solution and a TAX-co-AA-based nexus to rabbits. C_{max} was 30.3 $\pm$ 0.45 ng/mL after administration of the drug solution. In contrast, the C_{max} of TAX-co-AA-based hydrogel was 81.57 $\pm$ 0.35 ng/mL, which persisted for an extended period following the administration of TAX-co-AA-based hydrogel. The outcomes of in vivo studies were noteworthy, indicating that TAX-co-AA-based hydrogel improved the bioavailability of PE.

Table 1 shows the in vitro release studies of drugs and bioactive compounds from the macroscopic AX hydrogels described above.

3.1.1. Films

A property that AX present is their plasticizing capacity, which increases with the interaction of plasticizers, such as glycerol, sorbitol, or polyethylene glycol, allowing films to be obtained [107]. The intricate mechanisms underlying plasticization are elucidated in various ways in the literature. One explanation is the gel theory, positing that the polymer functions as a gel with non-covalent attraction points regulated by van der Waals forces and hydrogen bonds situated along adjacent chains. The primary impact of introducing a plasticizer is to displace or separate the attraction points, thereby enhancing mobility within the polymer system, considering that the plasticizers are fixed attraction points. In contrast, the mechanistic theory, a modified version of the gel theory, allows the plasticizer to move freely amidst the polymer chains undergoing plasticization [108].

The optimization of the formulation of AX-based films using central composite rotatable design (CCRD) has previously been reported to determine the optimal ratio of AX and plasticizing agent to create a mucoadhesive oral film for improving the delivery of tizanidine hydrochloride (TZN-HCl) [23,109]. The first study reported the synthesis of TAX through the esterification of AX with thioglycolic acid (TGA) to enhance its mucoadhesive potential. The mass ratio 1:6.66 of plasticizer (glycerol) to polymer (TAX) was appropriate for formulating a controlled-release mucoadhesive oral film of TZN-HCl. Afterward, the formulations were evaluated to determine their mechanical resistance, ex vivo mucoadhesion, as well as ex vivo permeation of TZN-HCl and in vitro release. From the results, satisfactory drug retention was noted during in vitro dissolution (85.03 % cumulative drug release) and ex vivo permeation (78.90 % cumulative amount of permeated drug) studies conducted over 8 h [23]. In the second study, the oral mucoadhesive films were made based on AX obtained from the husks of ispaghula (*Plantago ovata*). The formulation containing 300 mg of AX and 45 mg of glycerol showed a higher rate of TZN-HCl release (94.81 %) [109].

In another research, a pH/enzyme-responsive polymer film was obtained by solvent casting, mixing a pH-dependent acrylic polymer (Eudragit® FS 30 D) with AX isolated from gum psyllium. No chemical interactions between the Eudragit® FS 30 D and the AX's chains were demonstrated, thus implying that the film-forming polymer structure was derived from a physical mixture of both polymers. However, incorporating the AX exerted a significant impact on the average swelling index of the films. Additionally, the films loaded with AX are more responsive to pH fluctuations and prone to enzymatic degradation. The latter was observed when the AX-loaded films exhibited substantial weight loss upon immersion in a buffer solution containing the enzyme Pectinex® 3X-L. This

indicates the imprinting of the enzyme-dependent properties from AX onto the film formulation. Such a polymer film holds promise for applications in colon-specific drug delivery systems [110].

A film based on an arabinoxylan-rich fraction from brewers' spent grain (BSG-AX) was also reported. It was prepared using the solvent-cast method, employing glycerol as the plasticizer to evaluate its application as a bioactive compounds release matrix. Caffeine was chosen as a model compound because it is a hydrophilic active principle. The film made from BSG-AX and caffeine demonstrated favorable mechanical and morphological properties, indicating that it could be employed as a release matrix. Furthermore, during in vitro dissolution studies, caffeine was mainly released by diffusion control. It was attributed that the remaining caffeine could be released after the colonic microbiota degrades the BSG-AX film [27]. Something interesting in this study is that the AX were extracted from brewers' spent grain (BSG) from the brewing industry, which would allow the integration of this type of agri-food by-products within a circular economy.

Carbohydrate polymers are biological macromolecules that have garnered attention in wound healing for their sustained drug-release properties. The use of AX in preparing antimicrobial release films for wound healing has previously been reported. AX-based film dressings were prepared and characterized to evaluate their application as a gentamicin (GM) delivery system. The AX fraction employed in this study was extracted from *Plantago ovata* seed husk. After that, blank and gentamicin-loaded films were

Table 2
Drugs and bioactive compounds in vitro release studies using based AX films, tablets, and capsules.

Delivery system	Molecule tested	Release conditions	Final release percentage (%, w/v)	Reference
Mucoadhesive oral film containing: thiolated arabinoxylan (TAX) (320.70 mg), glycerol (48.10 mg), hydroxypropylmethylcellulose (HPMC) K15 M (2 mL of 2 % solution), and polysuccralose (1 mL of 2 % solution)	Tizanidine hydrochloride (TZN-HCl)	Dissolution testing (DT): use of United States Pharmacopeia (USP) dissolution apparatus 2 (paddle apparatus) (USP-PDA-II) at 37 ± 0.50 °C and 50 rpm Dissolution medium (DM): phosphate buffer (pH = 6.8) Maximum release time (MRT): 8 h	85.13	[23]
Mucoadhesive oral film containing: AX (300 mg), glycerol (45 mg), HPMC K15 M (2 mL of 2 % solution), and polysuccralose (1 mL of 2 % solution)	TZN-HCl	DT: use of USP-PDA-II at 37 ± 0.50 °C and 50 rpm DM: phosphate buffer (pH = 6.8) MRT: 8 h	94.81	[109]
Film based on an arabinoxylan-rich fraction from brewers' spent grain (BSG-AX) plasticized with glycerol	Caffeine	DT: 25 °C and 100 rpm tangential rotation DM: deionized water MRT: 7 h	97.76 ± 0.31	[27]
AX-based film plasticized with glycerol (AXFD3 formulation): AX (3 % w/v), glycerol (2 % w/v), and gentamicin (0.10 % w/v)	Gentamicin	DT: use of Franz diffusion cell (DHC-6T Transdermal System with a DHC-800 system controller from Logan Instruments Corp, Somerset, NJ, USA) at 37 °C DM: phosphate buffer (pH = 7.4) MRT: 12 h	90	[111]
AX, chitosan (CS), and reduced graphene oxide (rGO) films crosslinked using tetraethyl orthosilicate (TEOS)	Silver-sulfadiazine	DT: use of Franz diffusion cell at 37 °C DM: phosphate-buffered saline (PBS) solution at several pH values (6.4, 7.4, and 8.4) MRT: 24 h	58.30 (at pH 6.4) 93.10 (at pH 7.4) 53.71 (at pH 8.4)	[112]
Tablets-based on AX	Diclofenac sodium (DS) and caffeine	DT: use of USP-PDA-II at 37 ± 0.10 °C and 50 rpm DM: HCl buffer (pH 1.2), acetate buffer (pH 4.5), phosphate buffer (pH 6.8), phosphate buffer (pH 7.4) and distilled water. MRT: 15 h	64 (released DS in DDW) 38 (released DS at pH 6.8) 50 (released DS at pH 7.4) 76 (released caffeine in distilled water) 79 (released caffeine at pH 1.2) 84 (released caffeine at pH 4.5) 80 (released caffeine at pH 6.8) 80 (released caffeine at pH 7.2)	[115]
Tablets-based on dispersions of AX with Met-HCl (50 mg) and BSG-AX (150 mg), with different Ca^{2+} concentrations: F1: 0 mg (0 mol/L) F2: 415.17 mg (0.10 mol/L) F3: 830.34 mg (0.20 mol/L) F4: 1245.51 mg (0.30 mol/L)	Metformin hydrochloride (Met-HCl)	DT: 25 °C and 50 rpm tangential rotation DM: deionized water MRT: 6.5 h	% (w/v) of Met-HCl released at 6.5 h: 89.61 ± 1.17 (from F1), 82.10 ± 0.70 from (from F2), 67.74 ± 1.10 (from F3) and 30.86 ± 4.27 (from F4).	[117]
Hard gelatin capsules filled with BSG-AX and Met-HCl	Met-HCl	DT: 37 °C and 50 rpm tangential rotation DM: deionized water MRT: 6 h	70.981 ± 2.18	[17]

prepared using the solvent-cast method with glycerol as the plasticizer, varying the amounts of AX, glycerol, and gentamicin until determining the appropriate composition. Fourier-transform infrared spectroscopy (FT-IR) and differential scanning calorimetry (DSC) analysis confirmed the drug-film compatibility. AXFD3 showed the most suitable formulation for GM delivery to the wound site, constituted as follows: AX (3 % w/v), glycerol (2 % w/v), and GM (0.10 % w/v), as it can sustain the therapeutic GM level at the wound site for an extended duration. In an in vitro release study, 90 % of the GM was released from these films within 12 h. The antibacterial properties of the GM-loaded films closely resembled those of the standard GM solution. In addition, these films were found to be biodegradable and biocompatible. The cell viability assay indicated that the films were non-toxic, making them a promising material for dressing infected wounds. However, to enhance patient adherence to treatment, it is advisable to extend the GM release time of the films by cross-linking AX or integrating other biopolymers into the film formulations [111]. In another research, AX, Chitosan (CS), and reduced graphene oxide (rGO) films were crosslinked using tetraethyl orthosilicate (TEOS) as a crosslinker to create composite hydrogels and assessed their application as silver-sulfadiazine (SS) delivery-system for the wound dressing in the skin. Swelling index at various pH levels (1–3) indicated the pH sensitivity of the hydrogels. The controlled release profile of the SS, assessed at distinct pH values (4.5, 6.8, and 7.4) in phosphate-buffered saline (PBS) solution at 37 °C using the Franz diffusion method, demonstrated the maximum SS release (93.10 %, w/w) at pH 7.4 and 37 °C in 12 h [112]. Finally, in another research, AX was functionalized with graphene oxide (GO) via the hydrothermal method and cross-linked with polyvinyl alcohol (PVA) using various TEOS amounts to optimize hydrogel's properties and to get multifunctional composite hydrogels. In vivo assays were performed using a mouse full-thickness skin model, revealing accelerated wound healing within seven days without prominent inflammation and improved vascularization. Furthermore, the bergenin-loaded hydrogel exhibited a more pronounced effect on wound healing, contributing to the immediate healing process compared to the hydrogel alone [113].

Hence, composite hydrogels based on AX are promising as biomaterials for treating and caring for skin wounds. The applications of AX in forming films and coatings for drug delivery, described above, are shown in Table 2.

3.1.2. Tablets and capsules

Oral extended-release dosage forms (OERDF) are commonly fabricated with polymer-based monolithic matrix tablets. According to their role as retardants in drug release, polymeric materials used in their fabrication can be classified as hydrophilic, erodible, and insoluble. For OERDF fabricated with hydrophilic matrices, the controlled-release rate of drugs follows diffusion, swelling, and erosion mechanisms depending on the type and amount of drug and excipients, the preparation technique, the dimension and geometry of the DDS, and the environmental conditions during drug release. Reported phenomena that might be related to drug release in these matrices are (a) wetting of the system's surface with water, (b) penetration of the dissolution medium into the device, (c) glassy-to-rubbery-phase transitions of polymeric excipients, (d) polymer swelling, (e) drug diffusion, (f) polymer erosion, and (g) physical or chemical interactions between drugs and excipients [114].

Previously, tablets based on AX were reported to evaluate the release of caffeine and sodium diclofenac (DS) in different release media. It was observed that the tablets based on AX could provide sustained drug release depending on their solubilities and interactions with the drug-polymer. The comparable release profiles of caffeine in different media indicate a pH-independent release. However, the release of DS was significantly affected by its solubility. After comparison with a commercial pharmaceutical dosage form of DS, employing AX as the sustained release matrix displayed more favorable prospects in terms of efficacy, safety, and cost [115].

Drug release from tablets and capsules based on AX has also been evaluated in other investigations. For example, in one research, AX tablets were prepared with caffeine, atenolol, acetaminophen, lamivudine, mefenamic acid, lamotrigine, meloxicam, ibuprofen, flurbiprofen gliclazide, ofloxacin, piroxicam, salicylic acid, diclofenac, and famotidine; using the wet granulation technique. Powdered drug and AX were weighed separately in a 1:1 (w/w) ratio, homogenized, and the mixture was granulated. The tablets underwent a dissolution test in phosphate buffer (pH 7.4) employing the type II dissolving apparatus at 37 ± 0.10 °C y 50 rpm. The drugs showed different intervals in their release percentages in 12 h, being 75–85 % (for caffeine, atenolol, paracetamol, and lamivudine), 50–65 % (for ibuprofen and gliclazide), 26–42 % (for flurbiprofen, ofloxacin, piroxicam, salicylic acid, diclofenac, and famotidine), and 10–15 % (for mefenamic acid, lamotrigine, and meloxicam). Subsequently, a quantitative-structure-property relationship (QSPR) study on releasing these drugs from the tablets based on AX was reported using *ab initio* structure optimization and artificial neural networks (ANN). The authors computed a heuristic method (HM) and an unsupervised forward selection (UFS) of quantum mechanical, physicochemical, and structural descriptors for 16 drug molecules to pinpoint mechanistically related descriptors to response variables. QSPR models were established using multiple linear regression (MLR) and artificial neural networks (ANN) and validated by leave-one-out cross-validation and y-scrambling techniques. The models demonstrated robustness and high predictability regarding the release profile and mechanism of drug molecules from the AX matrix. In the case of release, descriptors such as softness, lipophilicity, unsaturation, atomic polarization, cyclic topology, and geometry of the drug molecules dictated the profile [116].

Another investigation determined the release percentage of metformin hydrochloride (Met-HCl) in deionized water from AX-based tablets with different Ca^{2+}. For this, dispersions of BSG-AX, Met-HCl and $CaCl_2{\cdot}H_2O$ were prepared, where the Ca^{2+} concentration was varied from 0 to 0.30 mol/L, which were later lyophilized, pulverized, and pressed to obtain tablets. It was observed that the Met-HCl release time increased as a function of the increase in the Ca^{2+}, concentration, having a release of up to 89.61 ± 1.165 % at 6.5 h for the tablet without Ca^{2+}; while, for the highest concentration of Ca^{2+} (0.30 mol/L) a 75.23 ± 3.422 % release of Met-HCl was obtained in 11.5 h. Therefore, the Ca^{2+} concentration also influenced the amount of Met-HCl released into the medium under the test conditions. These results were attributed to the formation of ionic bonds between the Ca^{2+} and the FA units linked by ester bond to the α-L-Ara*f* moieties, which produces crosslinking [117]. A mechanism for the formation of these bonds has previously been reported [118].

Finally, the release of Met-HCl from hard gelatin capsules filled with BSG-AX and Met-HCl was evaluated. The findings indicated

that BSG-AX acted as a release modifier for Met-HCl, a class III drug in the Biopharmaceutics Classification System (BCS), characterized by high solubility and low permeability through biological membranes. These results were attributed to the formation of hydrogen bonding between the AX chains and Met-HCl. AX, being a carbohydrate polymer, features polar OH groups in its structure. Conversely, MH molecules are stabilized by N–H···Cl and N–H···N hydrogen bonds. AX interacts with BCS class III drugs like atenolol, lamivudine, and famotidine through hydrogen bonding [17].

The applications of the AX in obtaining tablets and capsules to asses the in vitro release of drugs are shown in Table 2.

Table 3
In vitro release studies of drugs and bioactive compounds using multi-particulate systems, micro and nano hydrogels based on arabinoxylans.

Delivery system	Particle size	Molecule tested	Release conditions	Final release percentage (%, w/v)	Reference
Spheres based on arabinoxylans (AX)	549.54–661.23 μm	Gliclazide	Dissolution testing (DT): use of basket-type dissolution test apparatus (DR-08, Campbell Electronics, Mumbai) at 50 rpm and 37.50 ± 0.50 °C. Dissolution medium (DM): distilled water, 0.1 mol/L HCl, and phosphate buffer (pH 7.4). Maximum release time (MRT): 7.75 h (in distilled water), 8.16 h (in 0.1 mol/L HCl), and 6.50 h (in phosphate buffer).	90	[123]
Microspheres based on AX	>50 μm	Metronidazole hydrochloride	DT: use of United States Pharmacopeia (USP) dissolution tester TDT-08L (Electrolab, Mumbai, India) by the paddle method at 37 ± 0.50 °C and 50 rpm DM: 0.1 mol/L HCl MRT: 1.17–1.33 h	90	[124]
AX-sodium alginate beads	1.098–1.501 mm	Diclofenac sodium	DT: use of United States Pharmacopeia (USP) dissolution apparatus 2 (paddle apparatus) (USP-PDA-II) at 37 ± 0.50 °C and 50 rpm. DM: HCl buffer (pH 1.2) for 2 h and phosphate buffer (pH 6.8) for 6 h. MRT: 8 h	28.50	[125]
Microcapsules based on AX	15–40 μm	Microcrystalline copper (II)-aspirinate	DT: use of USP-PDA-II at 37 ± 0.50 °C and 60 rpm. DM: water, 0.1 mol/L HCl, and phosphate buffer (pH 8). MRT: 8 h	80 (in phosphate buffer at pH 8)	[126]
Core-shell AX gel particles	2.9 mm	Insulin	DT: use of a simulator of the human gastrointestinal tract (Simgi) at 37 °C in all compartments and with a simulation of the peristaltic movements.	24 (released before the particles reach the colon) 76 (released in the colon region)	[127]
Spheres based on AX with different formulations: F1: 0.06 insulin/AX mass ratio F2: 0.125 insulin/AX mass ratio F3: 0.250 insulin/AX mass ratio	320 μm	Insulin	DT: 37 °C under stirring (100 rpm). DM: Simulated gastric juice (SGJ) (USP–NF XXV, pH 1.2) for 2 h, then a simulated intestinal fluid (SIF) (USP–NF XXV, pH 6.5 and 7.4) for 8 and 14 h, respectively. MRT: 24 h	In SGJ: 25.8 % (from F1), 30.18 % (from F2), and 18.52 % (from F3) In SIF (pH 7.4): 38.8 % (from F1), 56.24 % (from F2), and 31.16 % (from F3)	[22]
Spheres based on AX	233 μm	Insulin	DT: use of a thermostatic bath at 37 °C under a stirring rate of 90 rpm. DM: HCl buffer (pH 1.2) for 2 h and phosphate buffer (pH 6.8) for 4 h.	18 (in HCl buffer (pH 1.2)) 20 (in phosphate buffer (pH 6.8))	[129]
Carboxymethyl arabinoxylan (CMAX)-chitosan polyelectrolyte complex nanoparticles	100 nm	Ibuprofen	DT: use of USP-PDA-II at 37 ± 0.50 °C and 50 rpm DM: Phosphate buffer (pH 7.2) MRT: 12 h	98.56	[84]
AX-doxorubicin (DOX) micelles with DOX core and AX shell	20–1000 nm	DOX	DT: 1 mL of micelles solution was transferred into dialysis bags (MWCO 3.5 kDa) and placed in 100 mL of release buffer at 37 °C. DM: Phosphate-buffered saline (pH 7.4 and 6.5) and acetate buffer (pH 4.5) MRT: 48 h	12.3 (at pH 7.4) 23.5 (at pH 6.5) 24.5 (at pH 4.5)	[131]

3.2. Multi-particulate systems, micro and nano hydrogels

Beyond unit dose distribution systems (UDDS) found in films, tablets, macro hydrogels, or capsules, there are also multi-particulate drug delivery systems (MDDS). MDDS comprises numerous independent units serving as drug carriers, collectively forming the complete dose. Typically, these multiple units have diameters ranging from micrometers (1–1000 μm) to millimeters (0.05–2.00 mm) and can take the form of granules, micro-particles (microspheres or micro-capsules), tablets (with a diameter of less than 3 mm), and pellets [119].

Microgels and nanogels are frequently employed for delivering hydrophobic drugs. Nevertheless, they can also provide advantages in overcoming various barriers associated with traditional drug delivery vehicles, owing to their water-swollen structure, size, deformability, colloidal stability, functionality, and physicochemical tunability [120]. Additionally, the use of microgels facilitates the control over essential characteristics such as functionality and size, which are vital to regulating drug binding and release kinetics precisely, ensuring long-term stability and shelf-life, addressing biocompatibility, manage biodistribution and targeting, address concerns related to bioaccumulation and degradation, and enhance functionality within the scope of a drug delivery application [121]. Methods for producing microgels are emulsification, complexation, homogeneous nucleation, and polymerization [96].

Previously, the obtaining of spherical particles based on AX prepared by enzymatic cross-linking was reported. The findings indicate that AX spheres demonstrated antioxidant activities in the ABTS radical scavenging test, suggesting their potential utilization as microencapsulation systems for antioxidants in various applications such as food, pharmacy, or cosmetics [122]. Applications of AX-based multiparticulate systems, micro and nano hydrogels to assess in vitro drug release are presented in Table 3 and described below.

In a previous investigation, some spheres were prepared based on AX obtained from Isabgol husk by employing the emulsification method with glutaraldehyde as a crosslinker to evaluate the release of gliclazide. An entrapment efficiency study revealed that approximately 89.73 % of applied gliclazide was loaded in Isabgol husk spheres. The objective was to assess the release of gliclazide in different dissolution media (distilled water, 0.1 mol/L HCl, and phosphate buffer at pH 7.4), comparing the release profile with conventional immediate-release tablets (Glizid 80®) containing gliclazide. The release pattern of gliclazide from crosslinked Isabgol husk microspheres differed from that of immediate-release tablets. While over 90 % of loaded gliclazide was released within 2–3 h from conventional immediate-release tablets, the release of gliclazide was slower from the spheres. The results were attributed to the swelling index of spheres in the different media. The swelling was observed to a lesser extent in 0.1 mol/L HCl than in distilled water and phosphate buffer (pH 7.4). The comparative results of the difference factor ($f1$) and similarity factor ($f2$) for gliclazide release from the spheres, when compared with Glizid 80®, exceeded the acceptable limits for bioequivalency. The outcomes of stable crosslinking, the sustained integrity of microspheres over an extended period, and the prolonged release of a model drug such as gliclazide underscore their applicability and potential for developing sustained-release formulations [123].

A previous report has documented the production of microspheres and beads containing AX sourced from *Plantago ovata*. The microspheres and beads were created using ionotropic gelation with calcium chloride as a crosslinker, and they were subsequently assessed for their effectiveness in drug release, specifically metronidazole hydrochloride (MH). The interactions between calcium and AX and the amorphous characteristics of the drug in the microspheres were substantiated through infrared spectroscopy and X-ray diffraction studies. Calcium-induced gelation prolonged the drug release to over 90 min in 0.1 mol/L HCl despite the high solubility of MH and the hydrophilic nature of AX [124]. In another investigation, composite beads of *Psyllium* AX and sodium alginate (SA) were prepared to assess the release of DS. According to the study's findings, the combined impact of SA-AX and calcium chloride had a notable impact on both the entrapment efficiency and the release of DS. The resulting beads exhibited an entrapment efficiency of 64.4 % and, throughout an 8-h study, released 28.5 % of the DS in a way consistent with zero-order kinetics and diffusion mechanism [125].

In another study, microcrystalline copper (II)-aspirinate was synthesized in situ in an AX obtained from the ispaghula (*Plantago ovata*) husk. This produced a slow-release device that sustained the release of the drug over 8 h in an alkaline environment, with the experimental data aligning with the Korsmeyer-Peppas model. The release rate followed the order: alkaline pH > distilled water > acidic pH, suggesting that the release of the drug from the AX depended on the environment's pH. This was attributed to the insolubility of the AX fraction in acidic mediums, which caused minimal swelling and significantly delayed release. These sustained profiles were in contrast to those of the unencapsulated drug. In addition, approximately 75 % of aspirin remains intact after passing through 0.1 mol/L HCl, which suggests that the device is excellent for delivering aspirin in the intestine [126].

Various investigations have reported the in vitro release of insulin from multi-particulate systems and micro hydrogels based on AX. For example, the creation and analysis of electro-sprayed core-shell particles comprising maize bran arabinoxylans (MBAX) with insulin in the core and maize wastewater arabinoxylans (MWAX) with *Bifidobacterium* in the shell were documented. These particles exhibited spherical shapes with an average diameter of 2.9 mm. Scanning electron microscopy (SEM) and confocal scanning laser microscopy (CSLM) verified the core-shell structure of the particles and the viability of entrapped probiotics. The encapsulation efficiency percentages for insulin and *Bifidobacterium* fall within the reported range for other encapsulation systems; these were 72 ± 28 and 90 ± 37 %, respectively. The study involved insulin degradation and release using a computer-controlled simulator of the human gastrointestinal tract (Simgi). The simulator comprises five successive reactors simulating the stomach (S), small intestine (SI), and the three regions of the colon: ascending (AC), transverse (TC), and descending (DC). All compartments were maintained at 37 °C with agitation to replicate peristaltic movements. The SI, AC, TC, and DC were kept under anaerobic conditions with a continuous nitrogen flow. The findings indicated that approximately 24 % of the insulin was released before reaching the colon, with the remaining 76 % predominantly released in the colon, particularly in cross-section. Moreover, an escalation in the *Bifidobacterium* population was observed, attributed to the fermentation of the particles by these bacteria in the colonic region. This suggests that AX microspheres could serve as a potential alternative for diabetes treatment [127].

In another investigation, a technique for the direct electrospray-induced creation of small composite microbeads, incorporating $CaCl_2$/ethanol-hardened low methoxy pectin and AX, was assessed. The model carried human recombinant insulin. The resulting core-shell beads exhibited stable spherical structures without signs of aggregation or coalescence. These beads featured a core containing insulin and AX, surrounded by a pectin shell. Optimal conditions yielded symmetrical and stable beads, with an average particle size of 1.02 ± 0.24 μm, and maintained stability without surface particle aggregation. Avoiding aggregation and coalescence is crucial as they contribute to polydispersity in microparticles and nanoparticles produced from various biopolymers. Consequently, the pectin/AX beads hold promise for future examinations involving degradation and insulin release under simulated conditions mimicking the human gastrointestinal tract. Furthermore, the authors recommended additional research to assess glycemic control through in vivo evaluations in animal models [128].

In a prior study, spheres of AX with various insulin/AX mass ratios were created by generating phenoxy radicals through the enzymatic oxidation of FA (entrapping insulin in situ). These spheres, with an average particle diameter of 320 μm, underwent investigation for insulin release behavior in simulated gastric juice (SGJ) and simulated intestinal fluid (SIF). Controlled in vitro release studies revealed that AX spheres minimized insulin loss in the upper gastrointestinal tract (GIT), retaining a substantial percentage (approximately 75 %) of insulin within their matrix. The reduced insulin release percentage could be attributed to the high cross-linking degree and swelling of the AX network. The outcomes indicated the effectiveness of these enzymatically cross-linked AX spheres as a novel carrier for oral insulin delivery [22]. Alternatively, obtaining AX-based spheres with a diameter of 233 μm has been reported using triaxial electrospraying. Spheres were loaded with a mixture of insulin and glutamic acid to adapt the size of insulin aggregates, where insulin trapped in the gelled spheres was unchanged during the AX gelation. An encapsulation efficiency of 71 % was achieved. The system was designed in the form of spheres to deliver oral insulin targeted to the colon. The formulation demonstrated stability in simulated gastric and small intestinal environments, exhibiting a low insulin release (20 %) under in vitro experimental conditions. Thus, results suggest that these spheres based on AX present promising prospects for developing oral drug delivery systems designed for proteins and peptide agents [129]. So far, it can be seen that covalent gels of AX exhibit minimal sensitivity to pH variations and are susceptible to fermentation by colonic microbiota. This characteristic renders them well-suited for oral insulin administration and targeted delivery to the colon. Due to their susceptibility to proteolytic degradation in the intestine, drugs derived from peptides and proteins are sought to be released in the colon for better absorption [130].

Regarding the nanogels, an earlier study documented the preparation of polyelectrolyte complex (PEC) nanoparticles utilizing CMAX and chitosan to assess its Ibuprofen release applications. A two-factor, three-level central composite design (CCD) was employed to investigate the effect of CMAX and chitosan concentrations on the PEC's particle size and particle size distribution. Under the optimal experimental conditions, a PEC with a size of 337.2 nm (predicted: 330.026 nm) and a polydispersity index of 0.335 (predicted: 0.224) was successfully obtained. However, when examining the morphology of the optimized PEC batch loaded with ibuprofen using transmission electron microscopy, it was observed that chitosan and CMAX particles interacted to form aggregates with ovoid to spherical shapes having a diameter of 100 nm. The PEC nanoparticles demonstrated sustained model drug release following Higuchi square root kinetics. From this research, it can be deduced that the interaction between CMAX and chitosan can be utilized to prepare nanoparticulate drug carriers [84]. Finally, another study used a biocompatible AX in medical applications to design a DDS for doxorubicin (DOX). DOX solubility was improved by forming hydrogen bonds with AX, creating an amphiphilic AX-DOX system: a micelle with a DOX core surrounded by an AX shell. DOX was rapidly released under low intracellular pH conditions, enhancing the in vitro cytotoxicity against MCF-7 cells, a human breast adenocarcinoma cell line. The release of DOX from AX-DOX micelles was contingent on the breakdown of hydrogen bonds and interactions between the drug and nanocarrier, which were influenced by the environmental pH. These findings suggest that the AX-DOX micellar formulation holds significant potential in cancer

Table 4
Most cited original research articles published in 1992–2022 of issues related to arabinoxylans and their uses as biomolecule release matrices, based on the Web of Science© Core Collection.

Paper title	DOI	Total Citations (TC)	TC per year
Intercellular adhesion and cell separation in plants	10.1046/j.1365–3040.2003.01034.x	256	12.80
Bioavailability of ferulic acid is determined by its bioaccessibility	10.1016/j.jcs.2008.12.001	163	11.64
Purification and Characterization of Enzymes Exhibiting β-D-Xylosidase Activities in Stem Tissues of Arabidopsis	10.1104/pp.104.041269	97	5.11
Feruloylated arabinoxylans and arabinoxylan gels: structure, sources and applications	10.1007/s11101-009-9147-3	84	6.46
Disintegration of wheat aleurone structure has an impact on the bioavailability of phenolic compounds and other phytochemicals as evidenced by altered urinary metabolite profile of diet-induced obese mice	10.1186/1743-7075-11-1	71	7.89
Influence of Non-Starch Polysaccharides Structure on the Metabolisable Energy of U.K. Wheat Fed to Poultry	10.1006/jcrs.1998.0213	64	2.67
Water stress and cell wall polysaccharides in the apical root zone of wheat cultivars varying in drought tolerance	10.1016/j.jplph.2007.09.006	63	4.20
Evaluation of hot-water extracted arabinoxylans from ispaghula seeds as drug carriers	10.1016/j.carbpol.2010.09.024	54	4.50
Psyllium Arabinoxylan: A Versatile Biomaterial for Potential Medicinal and Pharmaceutical Applications	10.1080/15583724.2015.1,078,351	46	6.57
Impact of the structure of arabinoxylan gels on their rheological and protein transport properties	10.1016/j.carbpol.2005.02.014	46	2.56

therapy [131].

4. Bibliometric analysis

4.1. Bibliometric mapping and analysis

Data gathering relied on scientific articles published and indexed on the Web of Science© (WoS) database. On December 27, 2022, a search was conducted on WoS to acquire the bibliographic information. Research in the WoS Core Collection was performed in the "advanced search" section using the following logical operation: TS = ('arabinoxylan*' AND 'release matrix' OR 'arabinoxylan*' AND

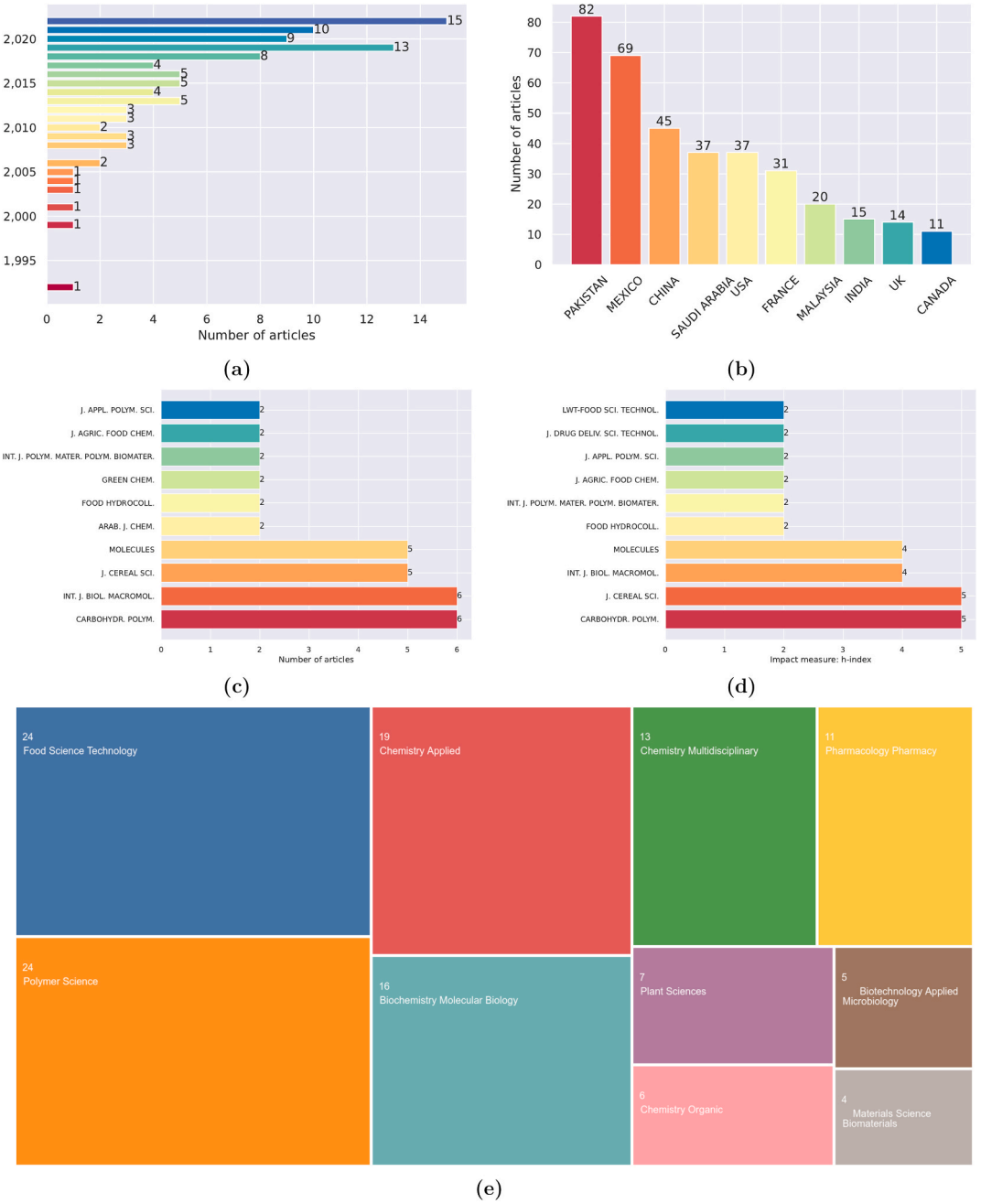


Fig. 3. Overview of scientific production from 1992 to 2022 timespan. (a) Annual scientific production. (b) Country scientific production. (c) Main reputed journals where articles were published. (d) Treemap chart of the number of publications in different disciplines according to the classification of Web of Science.

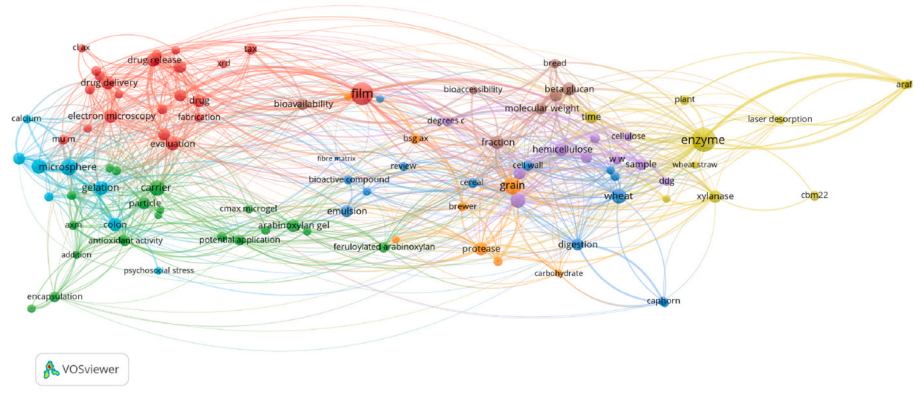
'delivery' OR 'arabinoxylan*' AND 'drug carrier') NOT KP = ('arabinoxylan*' AND 'release matrix' OR 'arabinoxylan*' AND 'delivery' OR 'arabinoxylan*' AND 'drug carrier'). A filtering process was implemented to refine the publications, considering specific words in the title, abstract, and author's keywords, excluding the keywords-plus associated with each document. This approach aimed to prevent discrepancies arising from words solely present in references that did not align with the primary focus of the study [132].

The analysis encompassed publications from 1992 to 2022, aligning with the configured timespan in the database. This ensured that the results reflected all the publications accessible in WoS during that period, resulting in a total of 102 documents, whose data were exported as BibTeX (dataset_wos.bib) and Research Information Systems (dataset_wos.ris) files using the option "Record Content: Full Record," to be analyzed with VOSviewer software v. 1.6.18 and with the software R-package bibliometrix version 4.0.1 [133] for the scientific mapping analysis, using the programming language R version 3.6.3 (2020-02-29) [134] and R-studio (version 2022.07.2) as integrated development environment [135]. The analysis was accomplished using the function bilbioshiny (-).

The WoS search resulted in 102 documents: 90 articles (1 is early access), 2 proceedings papers, 1 book chapter, and 9 reviews (1 is early access) from 1992 to the search date. Table 4 shows the top 10 globally cited documents during the studied timespan. As can be seen from the total number of citations, little research has been done on the subject. Fig. 3 provides an overview of the analysis.

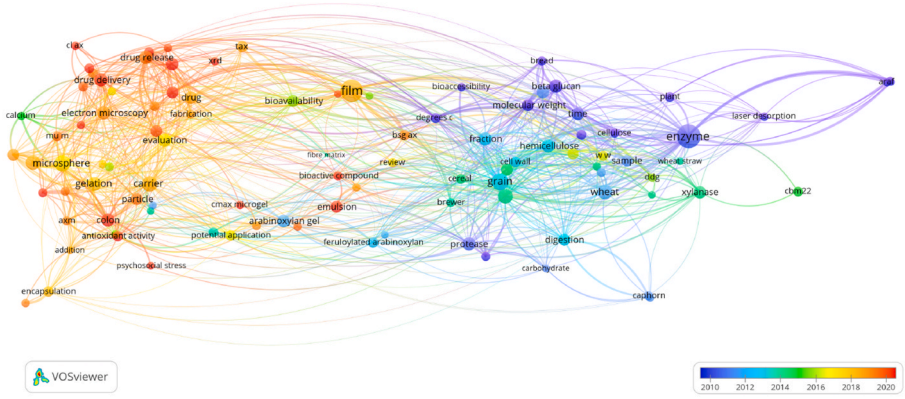
Fig. 3a illustrates the annual count of publications. The results show a rising pattern in publications each year from 1992 to 2022. In general, it can be noted that no research was carried out in the area from 1993 to 1998 and that since 2006, more articles have been published in this line of research. The years of greatest production were 2019 and 2022, with 13 and 15 publications, respectively. An

(a)

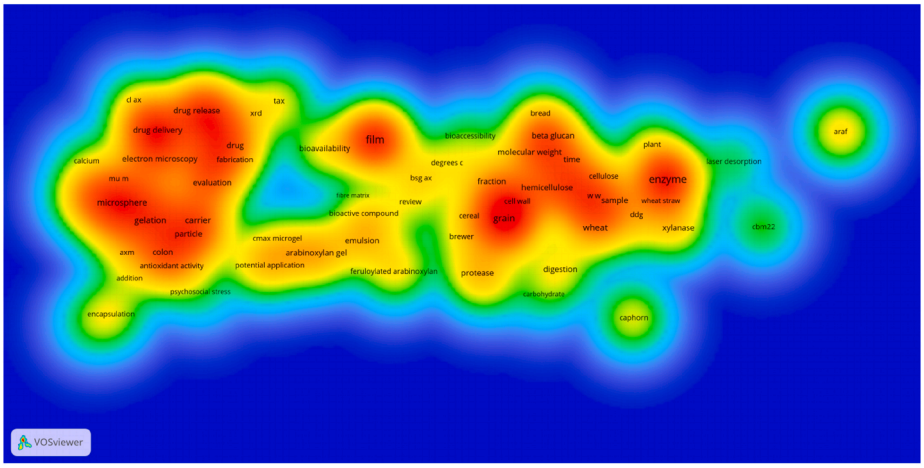


(b)

Fig. 4. Authors' keywords analysis from the period 1992–2022. (a) Word cloud containing the 50 principal authors' keywords. Scientometric mapping with the occurrence of the 101 principal authors' keywords: (b) network visualization, (c) overlay visualization, and (d) density visualization.



(c)



(d)

Fig. 4. (*continued*).

annual growth rate of 9.45 % was observed, which shows a remarkable space for development and research in the AX field and its applications as release matrices of bioactive compounds and drugs.

Fig. 3b displays the scientific output of different countries. Notably, the primary nations with higher publications on the subject during the studied timespan (alongside the corresponding publication counts) were as follows: Pakistan (82), Mexico (69), China (45), Saudi Arabia (37), USA (37), France (31), Malaysia (20), India (15), UK (14), and Canada (11).

Fig. 3c shows that the publications are in journals of different disciplines, mainly in Carbohydrate Polymers, International Journal of Biological Macromolecules, Journal of Cereal Science, and Molecules. In contrast, Fig. 3d shows the journals with the highest impact factor, using the h-index as a measurement parameter. This metric at the author level assesses the publications' productivity and citation impact. This coincides with the results obtained about the interdisciplinarity of the area computed from the WoS page (Fig. 3e). The topics have been studied more from the perspective of Food Science Technology (24), Polymer Science (24), Chemistry Applied (19), Biochemistry Molecular Biology (16), Chemistry Multidisciplinary (13), Pharmacology Pharmacy (11), Plant Sciences (7), Chemistry Organic (6), Biotechnology Applied Microbiology (5), Materials Science Biomaterials (4), Agriculture Multidisciplinary (3), and Engineering Biomedical (3), etc. Derived from these results, it can be observed that it is necessary to perform more research in the biomedical and pharmaceutical fields about the behavior of AX as release matrices to achieve its application in the DDS design and development so that the investigations are focused on the evaluation of its effects in vivo in addition to evaluating the functionality of the material as a release matrix.

4.2. Authors' keywords analysis

Fig. 4 displays the outcomes of the analysis of authors' keywords. Among the 102 examined publications, 366 authors' keywords

were identified. Within this set, the top 10 most commonly occurring authors' keywords are listed, along with the respective frequency (shown in parentheses): polysaccharides (17), release (17), in vitro (14), ferulic acid (13), gels (11), arabinoxylans (10), hydrogels (10), barley (9), drug-delivery (9), nanoparticles (9). A higher frequency of the keywords release and arabinoxylans were expected since they were used for the search. In Fig. 4a, a word cloud is presented, encompassing the 50 authors' keywords that were most frequently encountered in the outcomes of the WoS search. The word cloud is an essential tool for presenting a summary of the current literature on AX and its relationship to the topic of release matrices. The size of the letters represents the frequency of the keyword.

Fig. 4b–d shows the scientometric mapping, which was carried out with the software VOSviewer v. 1.6.18, using a modified methodology [136], as follows: (1) The selection of "create a map based on text data" was made. (2) The "Read data from reference manager files" option was chosen in the data source selection section. (3) The Research Information Systems text data file was loaded (dataset_wos.ris). (4) "Title and abstract fields" option was selected in the "Choose fields" section, ignoring structured abstract labels and copyright statements. (5) The counting method was configured to utilize full counting. (6) A threshold of five occurrences was established to ensure the inclusion of numerous concepts in the map. Of the 3243 terms, 169 meet the threshold. (7) The software calculated a relevance score for each of the 169 terms. Using this score, the terms deemed most relevant were chosen. The default option was chosen, consisting of 60 % of the most relevant terms, leading to a total of 101 terms. (8) The map was created. The normalization method chosen was the association strength. The cluster size was maintained at least one term per cluster, adhering to the default setting. The resolution parameter was set to one (default value). Finally, the map was exported as a PNG image file.

Fig. 4b displays 101 items, 8 clusters, and 1087 links, with a total link strength of 6377. The letters and circles' sizes indicate the frequency of occurrences, representing critical points in the selected research field. Distances between the keywords signify their connection through occurrence links, i.e., closer keywords have a closer relationship. The distances between the keywords can indicate gaps in knowledge areas. Therefore, it is necessary to carry out more scientific and technological research on the applications of AX to reduce information gaps. Nevertheless, given that the minimum threshold for the occurrences of authors' keywords is set at 5, these voids can be filled by incorporating other less frequently utilized keywords found in the literature [132]. Examining the frequency of keywords provides a meaningful approach to unveiling the primary content within the research field, which is why the words with the highest occurrence are considered hotspots in the area of AX research as release matrices.

The closely linked terms are organized into clusters, distinguished by the shared cluster color [137], with each cluster assigned a specific name (Table 5). According to the results, information has been reported on using AX in developing drug delivery systems and as biomolecule release matrices (cluster 1), the rheological AX hydrogels properties (cluster 2), the physicochemical AX characteristics (cluster 3), the extraction and enzymatic degradation of AX (cluster 4), the bioconversion of lignocellulose (cluster 5), the formulation of microspheres using AX for the controlled release of insulin in the colon. (cluster 6), the sources of extraction of the AX (cluster 7), and the nutritional and functional performance of β-glucans (cluster 8). This reflects that AX can be obtained by different extraction methods from distinct lignocellulosic materials, with biomass from various agri-food processes being a potential source to promote a circular economy [27], that allows taking advantage of lignocellulosic materials as raw materials to obtain functional compounds. It also emphasizes the importance of research focused on the physicochemical characteristics, extraction, and functional properties of AX. Additionally, it highlights the investigation into the formation of hydrogels from AX through enzymatic crosslinking and the study of its rheological properties. The latter is crucial, as it directly relates to the potential use of AX as biomolecule delivery matrices [63].

The VOSviewer software utilized a color scheme for keywords, associating them with the respective year of their appearance in the literature. Blue-colored keywords signified early appearances, followed by green and yellow, while keywords in orange and red indicated later appearances (Fig. 4c). Most words in cluster 1 were assigned in recent years, such as ax microcapsule, gelation, insulin, colon, evaluation, carrier, behavior, encapsulation, microsphere, particle, micro hydrogel, drug, drug release, and bioactive compound. Therefore, the study of polymeric matrices in the pharmaceutical field continues to be promising. Among the various nanodevices, polymeric matrix-based nanocomposites have emerged as highly promising and viable systems within the food industry [138] and drug nanodelivery systems [139]. Finally, the density map shows the citation concentration areas for keywords (Fig. 4d).

Following all of the above, the authors' keywords analysis showed that the selected area of knowledge had been studied in a multidisciplinary way, but the small number of items and occurrences indicate that there are information gaps, so it is necessary to study how the AX matrices could be applied in the development of DDS, to promote its possible application in the pharmaceutical industry.

Table 5
Clusters obtained in the scientometric mapping.

Cluster	Color (RGB color space)	Name	Items
1	Red (214, 39, 40)	Applications of arabinoxylans in the development of drug delivery systems	23
2	Green (40, 160, 44)	Arabinoxylans hydrogels and rheological properties	20
3	Blue (31, 119, 180)	Physicochemical properties	14
4	Fallout green (188, 189, 34)	Extraction and enzymatic degradation of arabinoxylans	11
5	Purple (148, 103, 189)	Bioconversion of lignocellulose	10
6	Cyan (23, 190, 207)	AX microspheres as insulin-releasing matrices in the colon	8
7	Orange (255, 127, 14)	Extraction sources of arabinoxylans	8
8	Brown (140, 86, 75)	Nutritional and functional performance of β-glucans	7

5. Concluding remarks and perspectives

This comprehensive review and bibliometric analysis have examined drug release studies over the last three decades, focusing on macro, micro, and nanogels based on AX and multi-particulate systems. The bibliometric analysis underscores the need for further exploration in this field, particularly emphasizing the scarcity of in vivo studies. While AX exhibits significant promise as a material for developing DDS, certain limitations challenge their progressive development. To address microbial contamination susceptibility, uncontrolled hydration rates, and limited understanding of drug release mechanisms, targeted modifications of AX through chemical, enzymatic, or physical means, including exploration of blends with other natural and synthetic polymers, are recommended. Specifically, future research efforts should prioritize the investigation of novel modification techniques that enhance AX's physicochemical profile, ensuring stability during storage and predictable drug release behavior.

Moreover, the future trajectory of AX-based DDS should consider tailoring formulations based on the specific requirements of drug solubility, dissolution speed, and biopharmaceutical properties. Rigorous studies exploring the impact of dissolution mediums on AX-based DDS performance and the correlation between drug characteristics and the selection of excipients during DDS development are crucial. In-depth investigations into these factors will provide valuable insights for optimizing pharmaceutical forms and enhancing the efficacy of AX-based drug delivery.

Finally, future research endeavors should focus on targeted modifications, explore synergies with other polymers, and conduct detailed studies on the interplay between drug characteristics and excipient selection to propel the development of AX-based DDS into a more robust and clinically applicable realm.

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Data availability statements

The data supporting this study's findings are available from the corresponding author upon reasonable request.

CRediT authorship contribution statement

Jesús Guadalupe Pérez-Flores: Writing – original draft, Software, Conceptualization. **Laura García-Curiel:** Writing – review & editing, Visualization, Software. **Emmanuel Pérez-Escalante:** Writing – review & editing, Methodology. **Elizabeth Contreras-López:** Resources, Conceptualization. **Enrique J. Olloqui:** Visualization, Investigation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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