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Review Article

HIBISCUS ROSA-SINENSIS MUCILAGE AS A FUNCTIONAL POLYMER IN PHARMACEUTICAL APPLICATIONS: A REVIEW

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ABSTRACT

The administration of drugs into the body is essential for the treatment of diseases. However, drugs need to reach the targeted site to be effective. Excipients such as polymers are used in drug formulations to ensure that drugs exert their therapeutic effects. Recently, plant-based polymers have been extensively explored in pharmaceutical research. These polymers, including gums and mucilages, are investigated for their roles in various pharmaceutical applications. The plant-based polymers have advantages compared to synthetic polymers due to their bioavailability, chemical inertness, non-toxicity and wide availability. When gums or mucilages are combined with other polymers, their final properties improve. In some instances, the characteristics of gums and mucilages such as swelling, flow and mucoadhesive properties are better than the abilities of synthetic materials. This article reviews the use of *Hibiscus rosa-sinensis* (HRS) mucilage as an excipient in several dosage forms to enhance drug delivery systems. Their physicochemical properties and mechanisms of action are also discussed. The review ends with a discussion of the limitations and future prospects of HRS mucilage in pharmaceutical applications.

Keywords: Gums and mucilages, *Hibiscus rosa-sinensis*, Polymer, Excipient, Pharmaceutical dosage form, Drug delivery

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INTRODUCTION

Drug administration is one of the primary topics in pharmacy. Ensuring drugs exert their action at the intended site has always been challenging for researchers in drug product development. Natural polymers have been extensively explored in pharmaceutical formulations, with polysaccharides frequently utilised as they have minimally invasive properties as drug carriers [1-3]. Gums and mucilages are heterogeneous polysaccharides. They exhibit high cohesive and adhesive properties as they are composed of complex branched polymeric structures [3]. These properties are advantageous since they frequently have a significant impact on drug release or absorption.

Gums and mucilages can be employed for a variety of reasons such as diluents, binders or disintegrants in tablets [4], thickeners in oral solutions, protective colloids in suspensions [5], gelling agents for gel dosage forms, bases for suppositories [6, 7], mucoadhesive agents in buccal drug delivery systems [8, 9] and as skin permeation enhancer in transdermal drug delivery system [10]. They are generally biocompatible, readily available, less toxic and do not irritate the skin [11].

Gums are formed upon external injury to a plant or due to unfavourable conditions such as drought, which cause the breakdown of cell walls (extracellular) [9, 12]. In contrast, mucilages are a typical physiological product of metabolism formed within the cell (intracellular) and can be produced without inflicting injury on the plant [9, 12]. Therefore, gums are characterised as pathological products, while mucilages are physiological products. Gums swell in water to form viscous and colloidal dispersions, whereas mucilages form slippery and aqueous colloidal dispersions. Mucilages are a substance that mainly consists of polysaccharides, proteins and uranides, and when in contact with water, they form a slimy mass.

Hibiscus rosa-sinensis (HRS) is a member of the family Malvaceae. It is known by many other names, such as rose mallow, China rose, musk mallow rose of Sharon and sour tea [12–14]. There are about 300 species in the family Malvaceae, found across the tropical region of the world, including in North Africa, China, Japan, Malaysia and Thailand [15, 16]. HRS is the most common species used in medicines. The presence of mucilage is typical in the Malvaceae, and its extraction is carried out from the leaves and flowers [17].

This article discusses the use of HRS mucilage in a variety of pharmaceutical dosage forms to improve drug delivery. In addition, their physicochemical features and mechanisms of action are reviewed. The database used to gather the related studies include the Web of Science Core Collection (1970-2022), Google Scholar (2010-2022), Science Direct (2010-2022), Scopus (2010-2022) and EBSCO: Medline Complete (2010-2022), using the following keywords: 'gums and mucilages', 'dosage forms', 'drug delivery systems', '*Hibiscus rosa-sinensis*', 'oral disintegrating tablets', 'mucoadhesive' and 'sustained release'. This article concludes with a discussion of the limitations and future potential of HRS mucilage in pharmaceutical applications.

HRS mucilage in pharmaceutical dosage forms and drug delivery systems

HRS mucilage can be obtained through the leaves and flowers of HRS species. Methylation analysis, partial hydrolysis and nuclear magnetic resonance studies show that the main structural features of HRS mucilage are due to its unique backbone chain composed of alpha-1,4-linked D-galactosyl, alpha-1,2-linked L-rhamnosyl and alpha-1,4-linked D-galacturonic acid units [18, 19]. HRS mucilage extract is a greenish-brown powder with a characteristic odour and amorphous nature. When dissolved in water, it provides a neutral, greenish-brown solution that is slimy and colloidal [17].

HRS mucilage is soluble in water but insoluble in methanol, ethanol, acetone and chloroform [17, 18]. The pH of HRS mucilage is generally 6.2, which is nearly neutral [17, 18, 20] and therefore will not irritate the mucosal membranes of the body. Drug-excipient compatibility studies have shown no significant interactions [6, 21–23], indicating that HRS mucilage can be used for a wide range of drugs.

Binding agent in tablets

Various types of mucilages are used as binding agents in pharmaceutical formulations. In comparison with synthetic compounds, mucilages show excellent binding properties [24]. HRS mucilage is able to attach to powder mass and convert it into

granules, which are further compressed into tablets. Based on a study by Bahadur *et al.* [25], HRS mucilage can be used as a binder in the formulation of glipizide tablets, an antidiabetic medicine. They determined that HRS mucilage has strong binding properties since drug release was delayed as mucilage concentration increased. In addition, Fourier-transform infrared (FTIR) spectroscopy analysis revealed that the drug (glipizide) and HRS mucilage were compatible (fig. 1).

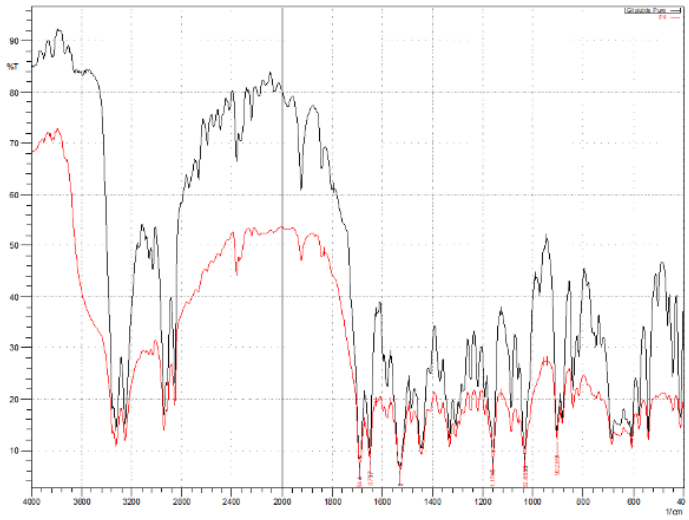

Fig. 1: FTIR spectra of pure glipizide and glipizide tablet formulation containing HRS mucilage [25]

Disintegrating agent in tablets

Tablets are the most popular orally administered dosage form. The main disadvantage of tablets is compliance for paediatric and geriatric patients, as well as patients who have swallowing difficulties (dysphagia). The development of orally disintegrating tablets or fast-dissolving tablets may aid in resolving these issues [21, 26]. This method of administration reduces swallowing effort and does not disrupt the airway [27]. When exposed to an aqueous environment, the disintegrating agent added to tablets and encapsulated formulations reduces the time required to break up the tablet or capsule shell into small fragments [21, 28]. Tablet disintegration can occur in four ways: swelling, porosity and capillary action (wicking), particle disintegration or repulsive particle force, and deformation [28, 29].

Swelling is believed to be the mechanism that imparts the disintegrating effect for HRS mucilage. When in contact with water, HRS mucilage swells up, which reduces the adhesiveness between the ingredients in the tablets and creates hydrodynamic pressure, thus causing the tablet to fall apart [21, 28]. Lakshmi *et al.* [18] conducted a comparative study between natural (HRS mucilage) and synthetic disintegrants (Kyron T-314, croscarmellose sodium and crospovidone) using levocetirizine as the active compound. The study showed that the time required for the tablet to disintegrate decreased as the concentration of HRS mucilage increased [6, 21]. Based on the findings, the following agents were ranked: Kyron T-314>crospovidone>HRS mucilage>croscarmellose sodium.

In addition, Shah and Patel [27] prepared and compared dispersible tablets of aceclofenac containing different concentrations of HRS mucilage at 2, 4, 6, and 8% w/w. HRS mucilage was found to be effective at a concentration of 4% (w/w), with a disintegration time of 20 seconds. It was concluded that a natural disintegrant like HRS mucilage has a better disintegrating property than the most commonly used synthetic superdisintegrants like croscarmellose sodium and crospovidone, and was on par with some other synthetic superdisintegrants like Kyron T-314 [21, 30]. As a result, HRS mucilage has the potential to be a promising superdisintegrant for tablets and other encapsulated formulations.

Gelling agent in gel dosage forms

Utilising natural gums and mucilages as a basis for pharmaceutical gels may be an innovative idea. Gums and mucilages can produce gels by themselves or in conjunction with other substances. Gelling is the outcome of several intermolecular and intramolecular interactions that form a three-dimensional network in which water molecules are entrapped [3].

Hydrogels, also known as aquagels, consist of a network of hydrophilic polymer chains that are dispersed in water to form a colloid. In tissue engineering, it can be utilised as a scaffold to repair injured tissue and as a controlled release system. Based on a study by Chaurasiya and Chakraborty [31], a concentration of 20% HRS mucilage was determined to be adequate for hydrogel formation in terms of physical properties such as neutral pH, with acceptable viscosity and spreadability.

Roy *et al.* [23] developed an in-situ nasal gel from HRS mucilage, using alprazolam as a model drug. In comparison to carbopol and hydroxypropyl methylcellulose (HPMC), HRS mucilage demonstrated superior bioadhesion to the nasal membrane due to its moderate swelling. In addition, the *in vivo* study suggested that HRS mucilage increased the bioavailability of alprazolam in comparison to synthetic polymers (fig. 2).

Modified-released formulations

There are numerous sustained-release systems, including dissolution-controlled release, which consists of encapsulation dissolution, seed or granule coating, microencapsulation, and matrix dissolution. In contrast, diffusion-controlled release utilises reservoir-type or matrix-type devices, diffusion and dissolution-controlled systems, ion-exchange resins, and osmotically-controlled release [32]. Nonetheless, matrix tablets, which are inexpensive and simple to produce, are the most often employed technology for oral sustained-release formulations [3].

The matrix system is a release system that extends and controls the movement of dissolved or dispersed drugs. Direct compression is used to create drug-embedded matrix tablets from a homogeneous mixture of active ingredients, retardant materials, and additives. Polymers are frequently used in matrix systems to modulate drug release. It is designed to continuously administer doses of a drug for an extended period of time, thereby maintaining the drug plasma level [33]. Gastro retentive drug delivery or floating tablets are also considered controlled-released systems because the drug is retained in the stomach after oral administration and releases the active ingredient in a controlled and sustained manner [34]. This mode of administration may be advantageous for the local treatment of disease in the stomach area.

The purpose of a modified released system is to improve the pharmacokinetics of the drug, increase patient compliance, and decrease side effects. The system is typically utilised for delayed release via enteric coatings, extended-release by biphasic release, programmed release, and time-or site-specific release [35]. Controlled-release devices can deliver a steady drug release at the chosen rate and duration. Ahad *et al.* [19] designed a sustained-release tablet of sodium diclofenac by employing HRS mucilage as a release retarding polymer. The results revealed that as the HRS mucilage content increased, so did the total release time of the drug from the matrix tablet. Such an increase in release time was related to the superior swelling and flow properties of HRS mucilage, demonstrating its compatibility with matrix formulations. The swelling index of mucilage was greatest in distilled water (5.13), followed by acidic (4.86) and alkaline environments (4.83) (table 1). The Carr index of HRS mucilage was low (9%), as well as the difference between the bulk and tapped densities (0.05). A lower Carr index value indicates fewer particle interactions and improved flow characteristics [17].

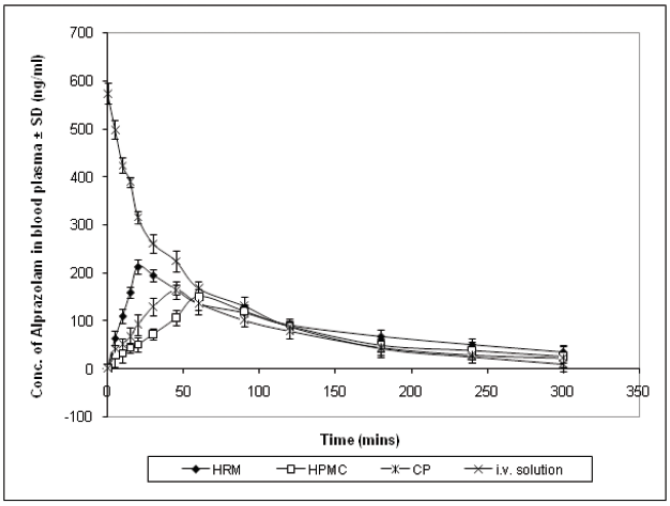

Fig. 2: Plasma concentration-time profiles of alprazolam following intravenous and in-situ nasal gel injection in rabbits (HRM: HRS mucilage; CP: Carbopol 934; i. v: intravenous injection) [23]

Table 1: Swelling ratio of HRS mucilage

Solvent	Swelling index	Reference
Distilled water	5.13	[17]
0.1N hydrochloric acid (HCl)	4.86	
0.1N sodium hydroxide (NaOH)	4.83	

In recent years, mucoadhesion has become a major topic in sustained-release formulations, notably for prolonging the retention duration in the stomach without altering gastric emptying time and with a continuous drug supply. According to studies, the performance of HRS mucilage is comparable to HPMC and carbopol when formulated into gastro retentive dosage forms [36, 37]. HRS mucilage has a swelling index of 4.86 in an acidic medium, which enhances its mucoadhesive property [17]. Mucilage's high viscosity and the negative charges on its surface also contribute to its mucoadhesive characteristic [17, 20]. In both studies by Kharwade *et al.* [36] and Palla *et al.* [37], HRS mucilage showed good compatibility with the active drugs employed, namely tramadol and domperidone, respectively. The findings also suggested that combinations of HPMC, carbopol and HRS mucilage significantly improved the mucoadhesive property, resulting in a prolonged retention period in the gastrointestinal region.

Stabilisers in emulsions and suspensions

In many pharmaceutical suspensions, stability is a challenge due to the interaction among different physical and electrochemical forces and the natural state of the suspended particles to aggregate and settle down [38]. A well-stabilised suspension should be able to quickly re-disperse upon shaking. The stability of a pharmaceutical emulsion is determined by the thin film that forms around dispersed globules by the emulsifying agent and its ability to resist rupture under pressure from approaching or coalescing droplets. Additionally, the formation of a mechanically strong coherent monolayer that acts as a barrier against the coalescence of dispersed oil droplets in an oil-in-water emulsion, or flocculation by particle bridges between adjacent oil globules whose surfaces are insufficiently covered by the film, is responsible for particle stability in stabilised emulsions [39].

Gums and mucilages can act as emulsifiers and suspending agents. They can effectively stabilise the emulsion through interfacial absorption, preventing droplet coalescence. They provide a degree of hydrophobicity that allows them to adsorb oil-in-water interfaces and stabilise emulsions via steric and electrostatic mechanisms [38, 40]. Natural gums and mucilages act as suspending agents by increasing the tensile strength of the hydration layer formed around suspended particles through hydrogen bonding and molecular interactions [3]. They are frequently used as protective colloids or thickeners, as their hydrophilic colloid structures facilitate dispersion in water and increase the viscosity of the continuous phase [41]. By increasing the viscosity of the vehicle, solid particles can remain suspended for a sufficient amount of time, ensuring the correct dose is administered.

HRS mucilage has the gelling polysaccharide property, allowing solvated polymer chains to extend to their maximum length and be firmly adsorbed onto dispersed particles or globules with numerous points of contact. According to Ash *et al.* [39], HRS mucilage at 1% w/v and 2% w/v concentrations incorporated into paediatric paracetamol suspensions possess good flowability, low sedimentation rate, and can be easily re-dispersed after sedimentation. HRS mucilage improves suspension stability by forming a protective coat around suspended drug particles and increasing the viscosity of the dispersing medium. Higher mucilage concentrations, on the other hand, resulted in decreased stability of sunflower oil emulsions (table 2). This instability could be caused by limitations in polymer chain extension, which results in the formation of an incomplete structural-mechanical barrier around the dispersed oil globules [39].

Table 2: Emulsion stability index (ESI) and emulsion activity index (EAI) of HRS mucilage-based paracetamol emulsions [39]

Batch	ESI at			EAI	Creaming rate	Globule size	Remarks
	24 h	72 h	120 h	(g. m^1 ml^{-1})	(cm/h)	(mean±SD) (µm)	
E1	2.75	11.80	34.23	2.248	0.0024	159.26±24.35	No flocculation and no coalescence
E2	3.43	7.43	28.29	2.063	0.0059	177.75±30.49	Slightly flocculated and no coalescence
E3	3.21	9.86	28.93	2.063	0.0107	316.11±54.83	Flocculated and no coalescence

HRS mucilage concentration: E1= 0.5% w/v; E2= 0.75% w/v; E3= 1.0% w/v.

Mucoadhesive agents in drug delivery systems

Mucoadhesive behaviour can be advantageous for nasal, buccal, and vaginal delivery. These formulations can form bonds with mucins in the mucosa, allowing for the continual release of the drug across the membrane. Many classes of polymers have been explored to determine whether they are suitable as mucoadhesive agents. A good mucoadhesive polymer has distinct properties such as hydrogen-bonding functional groups, suitable wetting property, swelling/water load capacity, and sufficient flexibility for entanglement with the tissue mucus network [42].

Mucoadhesion occurs due to interaction between mucoadhesive polymers and mucins. Mucins are essential for retaining hydration, providing lubrication and inhibiting microbe attachment [42, 43]. The formation of mucoadhesive bonds can be divided into two phases. In the first phase, when the mucoadhesive polymer comes into contact with water, it swells and expands into an irregular network with mucus, resulting in a double layer of mechanical interpenetration between the polymer and the mucus layer. The second phase involves chemical interactions between the polymer and the mucus layer [44].

Tyagi *et al.* [45] and Roy *et al.* [23] demonstrated the feasibility of using HRS mucilage for nasal gel mucoadhesive drug delivery. HRS mucilage exhibited better mucoadhesive qualities than HPMC and carbopol 934, which are two synthetic polymers commonly used in the preparation of nasal gels (table 3) [23]. In addition, the rheological and mechanical properties of HRS mucilage were superior to those of synthetic polymers. These benefits could be attributed to specific functional groups in the mucilage that allow it to make more intimate contact with mucosal mucins. Moreover, as HRS mucilage is a natural polymer, it does not cause unfavourable reactions in the nasal mucosa. The bioavailability of the drug was also enhanced with HRS mucilage compared to HPMC and carbopol 934 gels [23].

Table 3: Mucoadhesive strength of various nasal gels

Nasal gel formulation	Mucoadhesive strength (g)	Reference
HRM 5	67.56±0.34	[23]
HRM 10	75.25±0.55	
HRM 15	83.75±0.65	
CP 5	44.27±0.33	
CP 10	62.08±0.98	
CP 15	73.26±0.53	
HPMC 5	10.23±0.95	
HPMC 10	30.67±1.15	
HPMC 15	43.67±1.13	

HRM: HRS mucilage; CP: Carbopol 934.

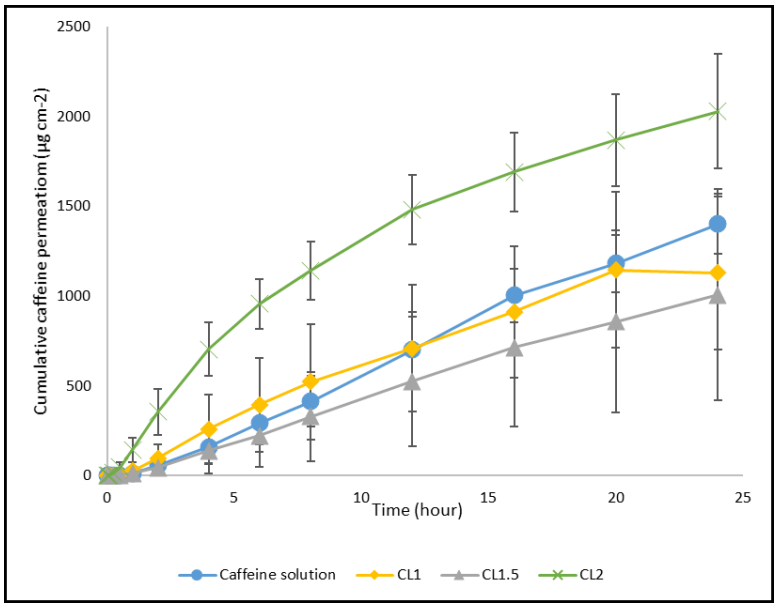

Fig. 3: Drug permeation profiles of caffeine solution and HRS gels. CL1: HRS mucilage 1% w/w; CL1.5: HRS mucilage 1.5% w/w; CL2: HRS mucilage 2% w/w. Reprinted by permission from springer nature: skin barrier modulation by *Hibiscus rosa–sinensis* L. mucilage for transdermal drug delivery [10], Copyright 2022

Skin permeation enhancer in transdermal drug delivery system

The permeation of drugs into the systemic circulation is largely restricted by skin layers, namely the epidermis (non-viable and viable), dermis (viable), and subcutaneous fat tissues, with the stratum corneum located at the epidermis's outermost layer serving as a significant barrier. Generally, drug permeation via the stratum corneum can be improved by disrupting the intercellular lipid matrix's structure, obstructing intercellular protein interaction, and increasing drug partitioning into the intracellular keratin domain [46]. These approaches include opening the tight junctions, altering keratin in proteinaceous corneocytes components, denaturing intercellular proteins, extracting lipid, increasing the lipid fluidity, creating diffusion channel, increasing the hydration within the stratum corneum, and increasing the drug's thermodynamic activity [46–48].

In a study conducted by Saidin *et al.* [10], it was discovered that HRS mucilage was effective in modifying the skin barrier for transdermal drug delivery using caffeine as the model drug. HRS mucilage at 2% w/w in gel dosage form demonstrated maximum drug permeation compared to pure caffeine solution and other HRS gels of lower concentrations (fig. 3). Further morphological and structural investigations suggested that HRS gels changed the skin permeability temporarily by disturbing the lipid and protein organisation, working on the helical keratin filaments and via the O-H and/or N-H interactions. The HRS gels were capable of extracting the skin lipid and interrupting the α-helices of protein hence altering the molecular arrangement to less rigid secondary structures and thereby increasing the drug permeability.

Limitations of HRS mucilage and future prospects

HRS mucilage is a naturally occurring polymer with superior swelling, flow, and mucoadhesive properties. It is also useful as suspending and emulsifying agents due to its high viscosity and ability to form a gel. Nonetheless, HRS mucilage has a number of limitations. The storage and packaging of HRS mucilage should be carefully selected to prevent microbial contamination [9, 35]. The risk of microbial contamination is high when mucilage is exposed to the external environment due to its high moisture content and carbohydrate structure. However, proper handling and use of preservatives can help to minimise contamination.

HRS mucilage is also associated with batch-to-batch variations; hence the quality of mucilage may vary between batches. This variation may affect the quality of HRS mucilage and result in differences in the activity or quantity of HRS mucilage. In addition, regional differences and climate conditions may influence the proportion of chemical constituents. Besides, viscosity is often reduced during storage owing to the complex nature of gums and mucilages [9, 35].

Despite the limitations, HRS mucilage has the potential to be a functional polymer in pharmaceutical dosage forms. When HRS mucilage is combined with other synthetic or natural polymers, the desired properties are enhanced, which in turn aids the drug delivery process. Several researchers have investigated the effects of combining HPMC and HRS mucilage [33, 49, 50]. Due to increased hydrophilicity, the HPMC/HRS mucilage combination demonstrated better swellability than the individual polymers. Moreover, in a study using ketoprofen matrix tablets [33], the combination of HPMC/HRS mucilage led to a greater drug release and better stability in terms of the dissolution rate, even after six months of storage at room temperature when compared to individual polymers.

CONCLUSION

In conclusion, the use of HRS mucilage in pharmaceutical dosage forms revealed numerous beneficial effects, either alone or in combination with other polymers. Furthermore, in some cases, combining HRS mucilage with other polymers improves their overall properties. More studies should be conducted, focusing on their mode of action to enhance our understanding and maximise the potential applications of HRS mucilage in a broader range of formulations.

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AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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