NATURALLY OCCURRING SWELLABLE POLYSACCHARIDES-BASED STIMULI-RESPONSIVE SMART TABLETS – A NEW WINDOW OF OPPORTUNITY

MUHAMMAD AJAZ HUSSAIN* and MUHAMMAD TAHIR HASEEB**

*Centre for Organic Chemistry, School of Chemistry, University of the Punjab, Lahore 54590, Pakistan
**College of Pharmacy, University of Sargodha, Sargodha 40100, Pakistan
✉ Corresponding author: M. A. Hussain, majaz172@yahoo.com

Received October 28, 2023

Currently, synthetic and semi-synthetic polymers are widely used in the development of various drug delivery systems (DDSs), biomedical and surgical devices, and healthcare materials. However, many drawbacks and problems are associated with these polymeric materials, including toxicity, immunogenicity, non-biodegradability, non-biocompatibility, and complicated, costly synthesis. To address such drawbacks, nowadays, naturally occurring swellable polysaccharides (NOSPs) are being evaluated for the possible replacement of synthetic polymers. NOSPs have shown remarkable stimuli-responsive properties, which made them an ideal material to develop stimuli-responsive DDSs, especially "smart tablets". The present review focuses on the summarization of stimuli-responsive properties (swelling, on-off switching, and drug release) of smart/stimuli-responsive tablets that respond to various stimuli, *e.g.*, pH, solvent, transit, time, *etc*. This article highlights the need to develop NOSPs-based smart tablets for intelligent and targeted drug delivery.

Keywords: hydrogels, biopolymers, polysaccharides, pH-responsive materials, smart tablets, on-off swelling, intelligent drug delivery

INTRODUCTION

Over the past few decades, synthetic polymers have been widely used in the field of medicine as pharmaceutical excipients and in biomedical devices, biotechnological products, and healthcare systems.[1-4] Several risk factors, environmental hazards, acute and chronic toxicity, and carcinogenic potential are associated with these synthetic polymers.[5-8] Therefore, a dire need for new materials to cope with all these drawbacks arises. Scientists are moving towards naturally occurring biomaterials due to their biodegradability, non-toxicity, non-immunogenicity, biocompatibility, easy availability, and cost-effectiveness.[9-12] Among biomaterials, naturally occurring swellable polysaccharides (NOSPs) are the most important materials due to their many applications in various fields, *e.g.*, biomedical sciences, food and agriculture sector, chemical and bioengineering, biotechnology, pharmaceutical industries, and DDSs.[13-17] NOSPs are biocompatible, non-toxic, non-immunogenic, and biodegradable due to their structural similarities to the extracellular matrix.[18,19]

Besides other biomedical applications, NOSPs are used as important excipients in tablet formulations to modify the release of active pharmaceutical ingredients (APIs). Additionally, NOSPs have the properties to respond differently to external stimuli, hence recognized as smart biomaterials. Therefore, this review aims to identify a new area in modern smart tablets prepared from NOSPs. This article is gathering the most recent information and commentary/opinion on this new type of DDSs, *i.e.*, stimuli-responsive smart tablets. This review will bridge the knowledge gap among researchers working in the development of smart/stimuli-responsive tablets and hydrogels, as well as formulation development from NOSPs for pharmacists and chemists working in academia and industry.

Naturally occurring swellable polysaccharides

Polysaccharides are long-chain carbohydrates mainly composed of monosaccharides connected through the glycosidic linkage. The number of monosaccharide units and the presence of different functional groups on these monosaccharides determine the nature and properties of these polysaccharides, *i.e*., the extent of solubility, cationic or anionic nature, hydrophilicity, hydrophobicity, *etc*. Despite the presence of hydrophilic groups on the backbone of these polysaccharides, the long-chain polysaccharides cannot dissolve in water. However, after water penetration, these polysaccharides swell and can retain a significant amount of water for a longer duration. Such swellable polysaccharides, *i.e*., NOSPs, have the properties of hydrogels and have ideally been used for the development of sustained or prolonged-release DDSs. Owing to the importance of NOSPs, the focus of the researchers has shifted to the development of different DDSs from these NOSPs, especially tablets.

Isolation/extraction of NOSPs

The isolation of NOSPs is carried out using different techniques either alone or in combination with each other. Some commonly used extraction methods include hot and/or cold water extraction, sonication, use of dilute alkali-water or acidic aqueous solution, enzymolysis, treatment with dimethyl sulfoxide or some organic solvents of alkali metal salts, *etc*.[20-23]

The seeds of a famous plant, flax/linseed (*Linum usitatissimum* L.), extrude rhamnogalacturonan polysaccharide (hydrogel/mucilage) upon soaking in hot water. The linseed hydrogel (LSH) appeared as a superporous and superabsorbent NOSP and showed pH-responsive swelling and deswelling attributes.[24] LSH exhibited swelling at pH 7.4 and deswelling at pH 1.2.

Another NOSP, glucuronoxylan, has been isolated from seeds of *Mimosa pudica* and *Cydonia oblonga* termed as *Mimosa pudica* hydrogel (MPH) or quince hydrogel (QH), respectively, which appeared as excellent smart materials for the development of stimuli-responsive smart tablets.[25,26]

Sweet basil (*Ocimum basilicum* L.) is a famous ornamental culinary herb and its seeds extrude mucilage (OBH) when in contact with water. The main constituent of the OBH is glucomannan, which has been explored recently for its pH-responsive swelling deswelling behavior at different pH values and sustained drug release properties.[27]

Artemisia vulgaris seeds hydrogel (AVH) is another valuable NOSP that has been explored for its stimuli-responsive properties and revealed that the swelling of AVH is dependent on the pH of the solvent. The swelling of AVH follows the trend: deionized water > pH 7.4 > pH 6.8 > pH 4.5.[28] A negligible swelling of AVH was observed at pH 1.2. Moreover, AVH has shown a significant swelling/deswelling property at pH 7.4 and 1.2.

Arabinoxylan is also a valuable NOSP, isolated from dietary fiber, *i.e*., psyllium (*Plantago ovata*), which also expressed swelling and deswelling attributes at pH 7.4 and 1.2, respectively, with sustained drug release behavior.[29]

Salvia spinosa seeds hydrogel (SSH) also responds differently to the physiological pH of the gastrointestinal tract (GIT). As the pH of the swelling media increases, the swelling of the SSH also increases. The maximum swelling was observed in deionized water (DW). The swelling of NOSP, *i.e*., SSH, followed the order: DW > pH 7.4 > pH 6.8. Negligible swelling was observed at pH 1.2.[30]

ENGINEERING OF SMART TABLETS

The usual trend in the pharmaceutical industry is mainly focused on the use of synthetic polymers in the development of different DDSs.[31-36] These systems include tablets (immediate release, sustained release, orodispersible), films (orodispersible, mucoadhesive), dermal and transdermal patches, microparticles, nanoparticles, *etc*. Several studies showed that there are many side effects/drawbacks associated with the use of synthetic polymeric materials, *e.g*., low biocompatibility, non-biodegradability, toxicity, carcinogenicity, cyst formation, immunogenicity, *etc*.

Due to the aforementioned disadvantages of the use of synthetic polymers in drug delivery applications, there is an alternative available in the form of NOSPs. Many advantages are associated with the use of these NOSPs, such as biocompatibility, stimuli-responsive nature, and high swelling ability (with on-off swelling behavior), which make them ideal candidates for the sustained release DDSs.[37]

The oral route is considered the safest route for drug administration and the tablets are the most prescribed DDS. Conventional tablets have now transformed into a novel shape known as smart tablets. The main ingredient of the smart tablets is any material that responds to external stimuli, *i.e.*, physiological conditions and imparts changes in its properties, especially on-off swelling that will lead to on-off drug release. Usually, these ingredients are NOSPs. Besides these water-swellable polysaccharides, *i.e.*, NOSPs, other pharmaceutical inactive materials are also used to make a smart tablet, as well as to keep the API in a dispensable form.

In recent studies, it was observed that several NOSPs possessed a high swelling capacity and after compression in tablet form, the swelling capacity reduces.[38] In tablet form, the interparticle spaces reduce due to the compaction, therefore, it is difficult for the media to penetrate the tablet, hence, the swelling of the tablet prepared using NOSPs reduces. However, in the case of a smart tablet, a significant increase in the swelling was observed for an extended time frame as surrounding media diffused slowly in smart tablets, hence sustained release can also be achieved alongside pH-responsive drug release. Literature also showed that, in such cases, the zero-order or first-order drug release from such NOSPs-based smart tablets was observed.[38,39]

pH-Responsive swelling and on-off switching

One of the factors influencing the release of drugs from DDSs is the surrounding physiological pH. Through the GIT, the DDSs have to face different pH values, from the acidic pH of the stomach to the slightly basic environment of the colon.[40,41] Therefore, one of the novel strategies is to develop NOSPs-based smart tablets that respond to the pH of the GIT and release drugs at the desired site.

NOSPs-based smart tablets are advantageous as NOSPs swell at neutral and near neutral pHs, while often showing almost off behavior in the stomach environment, *i.e.*, acidic pH. In this way, acid-sensitive drugs can be kept safe from the stomach environment. These polysaccharide materials have hydrophilic functional groups, *i.e.*, hydroxyls and carboxyls. In the buffer of pH 6.8 and 7.4, the carboxylic acid groups are converted to the anionic form and the electrostatic repulsion among these carboxylate anions resulted in the swelling of these polymers. Moreover, high swelling of these polysaccharides in deionized water, as compared to their behavior at pH 6.8 and 7.4, was witnessed in several recent studies, which can be explained due to the charge screening effect of the excessive cations (Na^+) present in the buffer solution.[42,43] The charge screening effect shielded these cations, which reduces the anion-anion repulsion due to the shielding of carboxylate anions. At pH 1.2, due to the protonation of carboxylate anions, the anion-anion repulsion diminished, hence, negligible swelling at pH 1.2 was observed. The reported NOSPs, *i.e.*, LSH, MPH, QH, OBH, AVH, psyllium hydrogel (PSH), and SSH-based tablets have shown significant swelling/deswelling behavior at pH 7.4 and 1.2, respectively (Fig. 1). Therefore, such materials are getting into the focus of researchers developing stimuli-responsive/smart tablets.

Salt-responsive properties

The swelling properties of the NOSPs are also dependent on the salt (NaCl) concentration in the swelling media. The osmotic pressure difference between the polymeric material and the media directly influences the swelling of NOSPs.[44,45] Due to the presence of salts in the GIT environment, the osmotic pressure in the GIT varies, which may result in variable swelling behavior of smart tablets, leading to variable drug release. Therefore, it is essential to determine the swelling capacity of the NOSPs and NOSPs-based smart tablets. It can be inferred that in a salt solution, less swelling will be observed for such smart tablets due to the charge screening effect of the excessive cations (Na^+) which reduces the electrostatic repulsion of the anions present in the polymeric chains. Another reason for the low swelling of these tablets in salt solutions is the neutralization of COO^- ions by K^+ and Na^+ ions, and electrostatic repulsion between the COO^- ions becomes low.[46]

As mentioned earlier, LSH, MPH, QH, OBH, AVH, PSH, and SSH-based tablets exhibit salt solution-responsive swelling.[38,39,28-30,47,48] Studies revealed that smart tablets based on the said NOSPs have shown an inverse relationship between swelling and the concentration of salts (NaCl and KCl). Additionally, these smart tablets also showed swelling/deswelling behavior in deionized water and normal saline, respectively (Fig. 1).

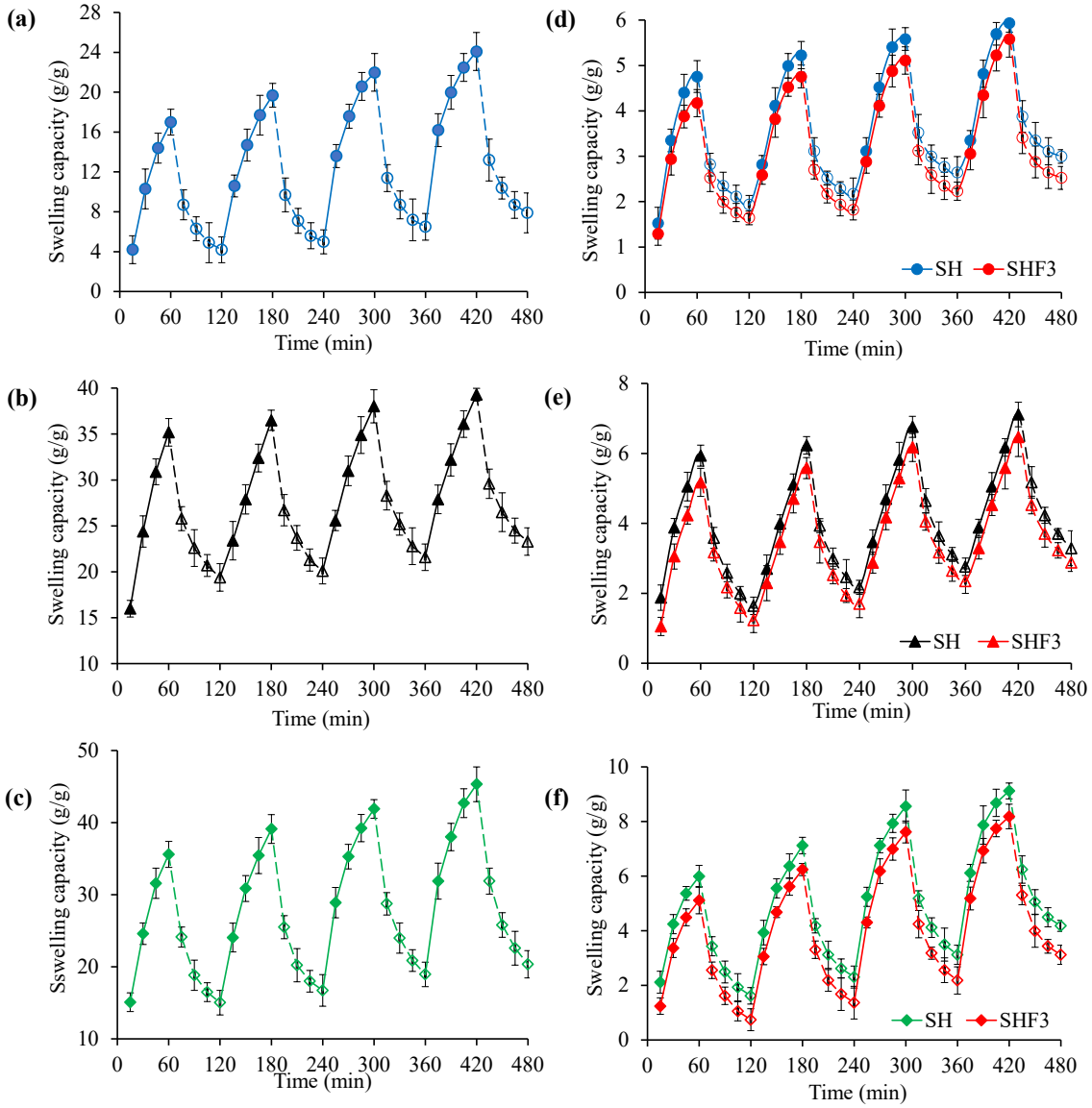

Figure 1: Swelling and deswelling of SSH (in powder form) and SSH-based tablet formulations (SH and SHF3) in a buffer of pH 7.4 and 1.2 (a and d), in DW and normal saline (b and e), and water and ethanol (c and f), respectively[30] (used with permission of Bentham Science Publisher; permission conveyed through Copyright Clearance Center, Inc.)

Solvent-responsive properties of NOSP-based smart tablets

Another important and recently explored property of NOSPs is their ability to respond to ethanol (a chemical mainly present in alcoholic beverages). The swelling and deswelling behavior of different NOSPs was observed by immersing the water-swollen NOSPs in ethanol. An abrupt deswelling of NOSPs was observed in various cases. The swelling and deswelling of NOSPs in water and ethanol, respectively, were observed to be also reversible. The swelling and deswelling pattern of these NOSPs was also witnessed when converted into tablet form. The tablets prepared with NOSPs, *i.e.*, LSH, MPH, QH, BSH/OBH, AVH, PSH, and SSH, expressed swelling and deswelling in water and ethanol, respectively (Fig. 1).[38,39,29,30,47-49]

The significant deswelling of the swollen NOSPs in ethanol is due to the lower affinity of NOSPs to ethanol, as compared to the water. Moreover, NOSPs form few hydrogen bonds with ethanol because of the low polarity and dielectric constant of ethanol (24.55), compared to that of water (80.40). As a result, the low dielectric constant decreases the ionization of the ionizable groups of the NOSPs and also reduces the swelling. Upon shifting the deswelled NOSPs in water, the ethanol molecules washed out quickly from the NOSPs and then formed extensive

hydrogen bonds with water.[38,39,28-30,47,48] Consequently, the swelling of NOSPs was observed again.

Therefore, the DDSs containing such NOSPs as inactive pharmaceutical ingredients should be administered with caution when administered with ethanol-containing beverages under the guidelines of the pharmacist, especially in sustained-release dosage forms. There may be some dose adjustments for patients with habitual alcohol intake.

Drug release studies from NOSPs-based smart tablets

As we have already discussed, NOSPs-based smart tablets may offer on-off swelling behavior with sustained release and intelligent drug delivery properties. Therefore, NOSPs are being used for the development of sustained/delayed/targeted drug-release tablet formulations. In a study, it has been noticed that the pH-responsive tablet formulation prepared with LSH released the drugs at pH 6.8 and 7.4, whereas it retarded the release of the drug at pH 1.2.[38] Moreover, by varying the concentration of glucuronoxylan, *i.e*., NOSP, the release of the drug was adjusted.[39,47] The OBH, another NOSP exhibited excellent properties to prolong the release of the drug for more than 8 h at intestinal pH.[48] In another study, AVH, *i.e*., NOSP, sustained the release of the drug up to 12 h (Fig. 2),[28] whereas PSH showed 24 h drug release.[29] Likewise, SSH sustained the release of the drug at pH 6.8 and 7.4 for more than 12 h.[30]

Table 1 describes the details of drug release kinetics and mechanism of drug release from different NOSPs. It was observed that drug release from different NOSPs (QH, OBH, MPH, AVH, and SSH) followed mostly the zero-order drug release.[28,30,39,47,48] In zero-order kinetics, the drug release is constant or uniform per unit time or the release is independent of the concentration of the drug in a polymeric system.[50] Moreover, drug release from QH, OBH, MPH, AVH, and SSH followed the super case-II transport, *i.e*., erosion-based mechanism.[51,52]

Drug release kinetics from LSH and PSH followed the first-order kinetics, which is a concentration-dependent process of drug release from a porous polymeric system.[50,53] Additionally, the drug release from LSH and PSH-based tablet formulations followed the non-Fickian diffusion mechanism.[51,52]

MRI, X-ray and SEM analyses of some NOSPs-based smart tablets

The pH-responsive swelling of the NOSPs-based smart tablets was also observed through magnetic resonance imaging (MRI) in a previous study (Fig. 3A).[28] The black and white region in the MRI images of the AVH-based tablets indicated the presence of low and high-intensity ^{1}H region, which corresponded to the absence and presence of water, respectively.[28] The increase in the intensity of the white region over time confirmed the penetration of water and swelling of the tablet.[54] The swelling study through MRI was performed for AVH-based tablets, caffeine, and levosulpiride-loaded AVH tablets, and comparable swelling behavior of all three formulations was observed during the whole course of the study, *i.e*., 8 h. In another MRI study, AVH-based tablets were unable to swell at pH 1.2, as indicated through the dark portion of the tablet during the 8 h study. Similar swelling behavior was noticed for OBH-based smart tablets in the MRI study. These MRI images proved that the NOSPs are generally unable to swell in acidic pH media (stomach pH), while swelling at the pH values of the small intestine. Hence, such NOSPs can be used for the site-specific delivery of many therapeutic agents.

The fate of the NOSP-based tablets during the transit through the GIT has been witnessed using an X-ray study (Fig. 3B). Barium sulfate was used as an opaquant in the tablet formulation and the swelling of the tablet in different segments of the GIT, as well as transit duration, was observed through X-ray studies using dog models. The studies also proved a good experimental model for the determination of the fate of tablets through the GIT, swelling behavior, and the degradation possibility in different segments and at various pH.[48,49]

The NOSPs can absorb and retain a large quantity of swelling media. The absorbency of the swelling media by NOSPs is possibly due to their porous structure. The morphology of the external as well as internal networking of the polymeric chains of these NOSPs has been examined through scanning electron microscopy (SEM) images in various studies (Fig. 3C).

Water swollen then freeze-dried samples of these NOSPs indicate diverse morphology depending upon the chemical composition of these polysaccharides. Therefore, one can observe elongated porous and multilayer channels,[24] interconnected macropores in MPH,[25] the hollow

porous structure of QH,[26] well-dispersed spongy pores in OBH,[27] uniformly dispersed thin wall micropores in AVH[28] and wide networking of elongated channels of PSH in the NOSPs.[29]

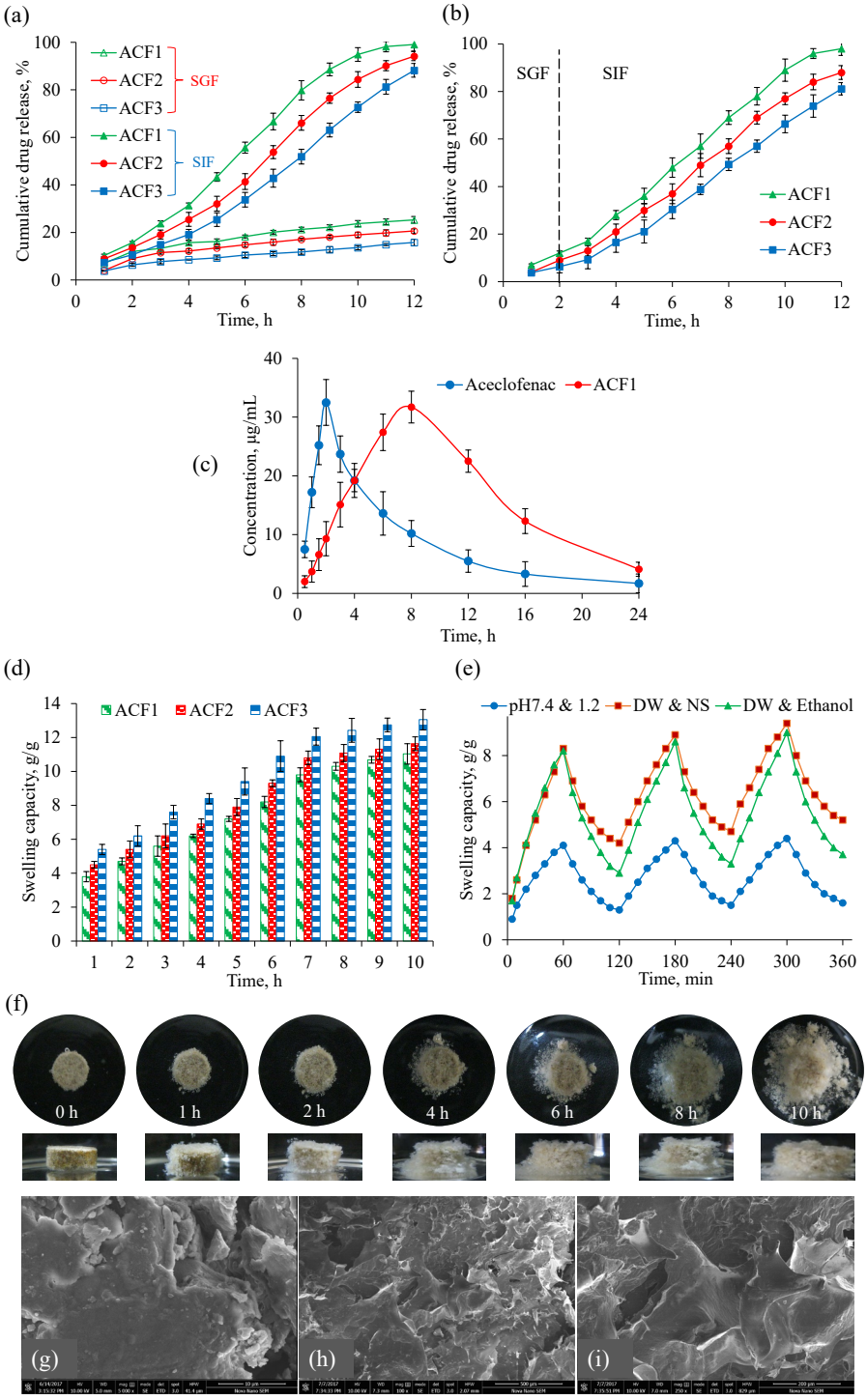

Figure 2: Aceclofenac release studies from AVH-based formulations (ACF1, ACF2, and ACF3) in simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) for 12 h (a), and in SGF (first 2 h) and SIF (remaining 10 h) (b), pharmacokinetic parameters of ACF1 tablet formulation (c), swelling capacity of three tablet formulations at pH 7.4 after various time intervals (d), stimuli-responsive swelling/deswelling of ACF1 at pH 7.4 and 1.2, in DW and normal saline (NS), and DW and ethanol (e), radial and axial view of the swelling of AVHF tablet at different time intervals in pH 7.4 buffer (f), and scanning electron micrographs of AVH tablet surface (formulation ACF3) (g) and tablet surface after swelling in water (h and i);[28] (reproduced with permission from the Royal Society of Chemistry)

Table 1
Detailed description of smart tablet formulations using NOSPs

Polysaccharides	Drugs	Swelling media	Deswelling media	Swelling and deswelling attributes	pH-responsive order of drug release	Sustained drug release duration	Drug release kinetics and mechanisms	Ref.
Linseed hydrogel (LSH) (rhamnogalacturonan)	Caffeine and Diacerein	pH 6.8, 7.4, and DW	pH 1.2, salt solution (NaCl and KCl), and ethanol	pH 7.4 and 1.2. DW and normal saline. DW and ethanol	Caffeine = DW > pH 7.4 > 6.8. Diacerein = pH 7.4 > 6.8 > DW	> 24 h	First-order kinetics and non-Fickian diffusion	[38]
Quince seed hydrogel (QH) (glucuronoxylan)	Theophylline and Diclofenac sodium	pH 6.8, 7.4, and DW	pH 1.2, salt solution (NaCl and KCl), and ethanol	pH 7.4 and 1.2. DW and normal saline. DW and ethanol	Theophylline = DW > pH 7.4 > 6.8. Diclofenac sodium = DW > pH 7.4 > 6.8.	> 12 h	Zero-order kinetics and super case-II transport	[39]
Mimosa pudica hydrogel (MPH) (glucuronoxylan)	Theophylline and Levosulpiride	pH 6.8, 7.4, and DW	pH 1.2, salt solution (NaCl and KCl), and ethanol	pH 7.4 and 1.2. DW and normal saline. DW and ethanol	Theophylline = DW > pH 7.4 > 6.8. Levosulpiride = DW > pH 7.4 > 6.8.	> 16 h	Zero-order kinetics and super case-II transport	[47]
Artemisia vulgaris hydrogel (AVH)	Caffeine and Levosulpiride	pH 6.8, 7.4, and DW	pH 1.2, salt solution (NaCl and KCl), and ethanol	pH 7.4 and 1.2. DW and normal saline. DW and ethanol	Caffeine = DW > pH 7.4 > 6.8. Levosulpiride = DW > pH 7.4 > 6.8.	> 12 h	Zero-order kinetics and super case-II transport	[49]
Ocimum basilicum L. (basil seed hydrogel) (OBH)	Theophylline and Domperidone	pH 6.8, 7.4, and DW	pH 1.2, salt solution (NaCl and KCl), and ethanol	pH 7.4 and 1.2. DW and normal saline. DW and ethanol	Theophylline = DW > pH 7.4 > 6.8. Domperidone = DW > pH 7.4 > 6.8.	> 12 h	Zero-order kinetics and super case-II transport	[48]
Plantago ovata (psyllium) hydrogel (PSH)	Theophylline	pH 6.8, 7.4, and DW	pH 1.2, salt solution (NaCl and KCl), and ethanol	pH 7.4 and 1.2. DW and normal saline. DW and ethanol	-	> 24 h	First-order kinetics and non-Fickian diffusion	[29]
Salvia spinosa hydrogel (SSH)	Theophylline	pH 6.8, 7.4, and DW	pH 1.2, salt solution (NaCl and KCl), and ethanol	pH 7.4 and 1.2. DW and normal saline. DW and ethanol	Theophylline = DW > pH 7.4 > 6.8.	> 12 h	Zero-order kinetics and super case-II transport	[30]

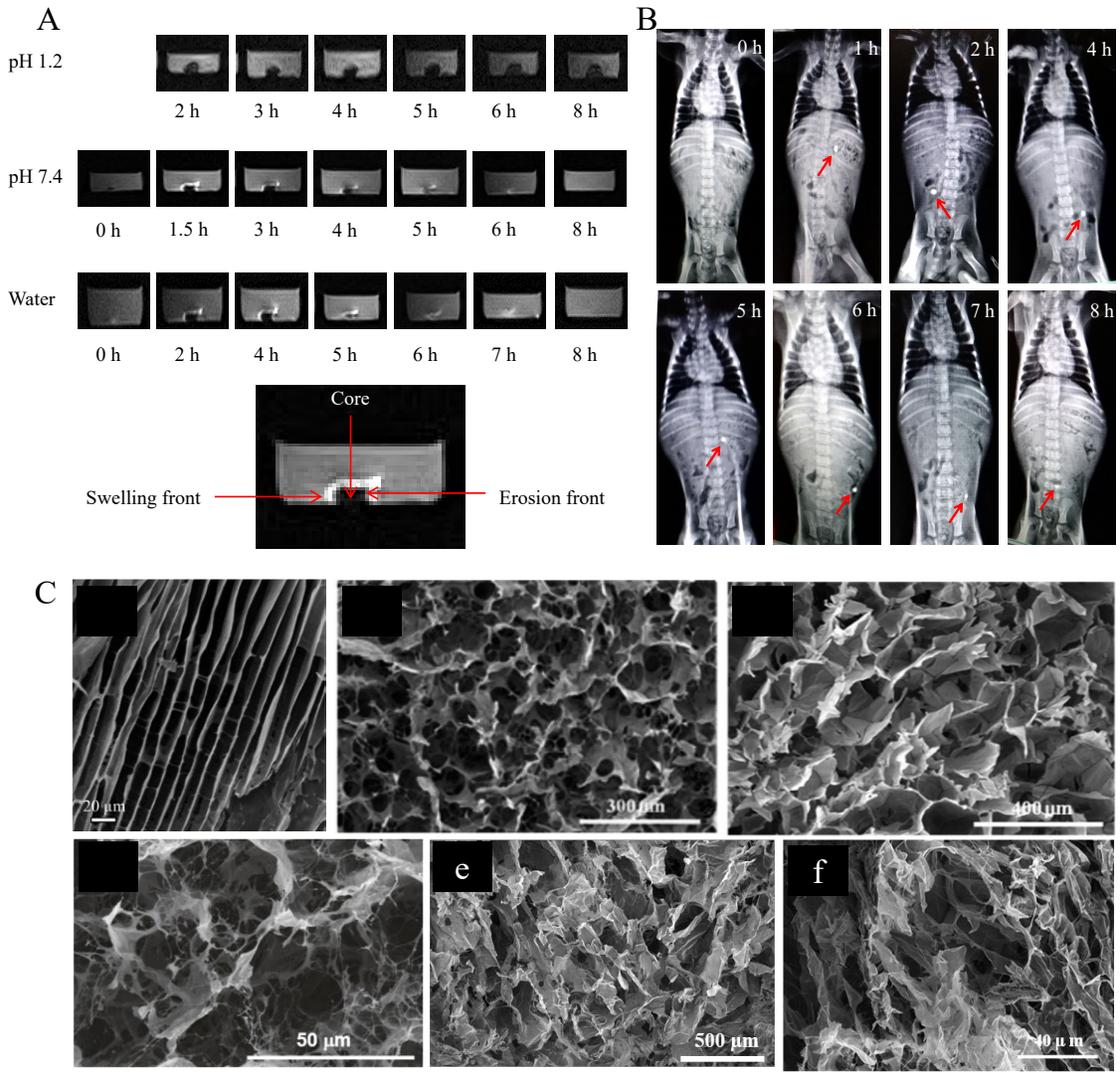

Figure 3: MRI images (A) of swelling behavior of AVH tablets (AVHM) in water, at pH 1.2 and 7.4 after different time intervals[28] (reproduced with permission from the Royal Society of Chemistry); *In-vivo* X-ray studies (B) of *Ocimum basilicum* hydrogel (OBH) containing tablets without drugs (FOBH) to track the position of prepared tablets in different segments of the gastrointestinal tract after various time intervals[48] (reprinted with permission from Elsevier); SEM images (C) of the cross-section of water-swollen then freeze-dried samples of LSH (a)[24] (reprinted with permission from Elsevier), and MPH (b)[25] (reproduced with permission from the Royal Society of Chemistry), QH (c)[26] (reprinted with permission from Elsevier), OBH (d)[27] (reproduced under Creative Commons Attribution License), AVH (e)[28] (reproduced with permission from the Royal Society of Chemistry) and PSH (f)[29] (reproduced with permission from the Royal Society of Chemistry)

Interestingly, these specific morphologies of the NOSPs are even retained to a good extent when formulated in tablet form, as witnessed from the literature. As a result, the specific characteristics of NOSPs (pH-dependent swelling and stimuli-responsive swelling/deswelling) are retained even after compression.

CONCLUSION AND THRUST AREAS

NOSPs have proved to be a stimuli-responsive material for pH-dependent, site-specific, and targeted DDSs. The inability of NOSPs to swell and release the drug at the pH of the stomach makes them an ideal candidate for the delivery of acidic drugs, especially non-steroidal anti-inflammatory drugs and protein-based drugs through the GIT. Such DDSs are very helpful to protect the mucous membrane of the GIT from the adverse effects of these acidic drugs, as well as to shield the protein-based drugs from degradation at acidic pH and in the harsh environment of the stomach. NOSPs could also be

used for the sustained release delivery of many APIs, including antibiotics, antiviral, antifungal, anticancer, *etc*. The detailed chemical structure, type and intensity/density of crosslinking, and nature of bonding among different molecules and functional groups of some of the reported NOSPs are still obscure. Moreover, a thorough and complete sugar analysis of some of these NOSPs has not yet been explored. As these NOSPs are biocompatible, biodegradable, non-immunogenic, and non-toxic, they could be used for wound healing, tissue engineering, scaffolds for bone regeneration, and other biomedical applications.

REFERENCES

[1] E. J. Bolívar-Monsalve, M. M. Alvarez, S. Hosseini, M. A. Espinosa-Hernandez, C. F. Ceballos-González *et al*., *Mater. Adv*., **2**, 4447 (2021), https://doi.org/10.1039/D1MA00092F

[2] C. Englert, J. C. Brendel, T. C. Majdanski, T. Yildirim, S. Schubert *et al*., *Prog. Polym. Sci*., **87**, 107 (2018), https://doi.org/10.1016/j.progpolymsci.2018.07.005

[3] C. Rivera-Hernández, M. Antunes-Ricardo, P. Martínez-Morales, M. L. Sánchez *et al*., *Int. J. Pharm*., **600**, 120478 (2021), https://doi.org/10.1016/j.ijpharm.2021.120478

[4] Y. K. Sung and S. W. Kim, *Biomater. Res*., **24**, 12 (2020), https://doi.org/10.1186/s40824-020-00190-7

[5] M. S. B. Reddy, D. Ponnamma, R. Choudhary and K. K. Sadasivuni, *Polymers*, **13**, 1105 (2021), https://doi.org/10.3390/polym13071105

[6] B. Li, Z. Yuan, H.-C. Hung, J. Ma, P. Jain *et al*., *Angew. Chem*., **57**, 13873 (2018), https://doi.org/10.1002/anie.201808615

[7] S. Anju, N. Prajitha, V. S. Sukanya and P. V. Mohanan, *Mater. Today Chem*., **16**, 100236 (2020), https://doi.org/10.1016/j.mtchem.2019.100236

[8] M. Jurak, A. E. Wiącek, A. Ladniak, K. Przykaza and K. Szafran, *Adv. Colloid Interface Sci*., **294**, 102451 (2021), https://doi.org/10.1016/j.cis.2021.102451

[9] M. Puertas-Bartolomé, A. Mora-Boza and L. García-Fernández, *Polymers*, **313**, 1209 (2021), https://doi.org/10.3390/polym13081209

[10] F. Piazza, M. Colella, G. Cinelli, F. Lopez, I. Donati *et al*., *Biomimetics*, **7**, 141 (2022), https://doi.org/10.3390/biomimetics7040141

[11] A. R. Allafchian, S. A. H. Jalali and S. E. Mousavi, *IET Nanobiotechnol*., **12**, 1108 (2018), https://doi.org/10.1049/iet-nbt.2018.5071

[12] H. Urena-Saborio, E. Alfaro-Viquez, D. Esquivel-Alvarado, S. Madrigal-Carballo and S. Gunasekaran, *Int. J. Biol. Macromol*., **115**, 1218 (2018), https://doi.org/10.1016/j.ijbiomac.2018.04.129

[13] B. Nikforouz, A. Allafchian, S. A. H. Jalali, H. Shakeripour and R. Mohammadinezhad, *Nanotechnology*, **33**, 075102 (2022), https://doi.org/10.1088/1361-6528/ac3576

[14] A. A. A. El-Maksoud, A. I. A. Makhlouf, A. B. Altemimi, I. H. A. El-Ghany, A. Nassrallah *et al*., *Molecules*, **26**, 6372 (2021), https://doi.org/10.3390/molecules26216372

[15] R. Kamel, S. M. Afifi, I. A. A. Kassem, N. A. Elkasabgy and M. A. Farag, *Int. J. Biol. Macromol*., **165**, 2550 (2020), https://doi.org/10.1016/j.ijbiomac.2020.10.175

[16] M. Shahid, H. Munir, N. Akhter, N. Akram, F. Anjum *et al*., *Int. J. Biol. Macromol*., **191**, 861 (2021), https://doi.org/10.1016/j.ijbiomac.2021.09.126

[17] D. T. Gaikwad, S. J. Patil and S. G. Killedar, *Nat. Prod. Res*., **29**, 1 (2022), https://doi.org/10.1080/14786419.2022.2140154

[18] M. Jin, J. Shi, W. Zhu, H. Yao and D. A. Wang, *Tissue Eng. B: Rev*., **27**, 604 (2021), https://doi.org/10.1089/ten.teb.2020.0208

[19] E. Rosellini, Y. S. Zhang, B. Migliori, N. Barbani, L. Lazzeri *et al*., *J. Biomed. Mater. Res. A*, **106**, 769 (2018), https://doi.org/10.1002/jbm.a.36272

[20] L. Shi, *Int. J. Biol. Macromol*., **92**, 37 (2016), https://doi.org/10.1016/j.ijbiomac.2016.06.100

[21] E. S. Morais, A. M. d. C. Lopes, M. G. Freire, C. S. R. Freire, J. A. P. Coutinho *et al*., *Molecules*, **25**, 3652 (2020), https://doi.org/10.3390/molecules25163652

[22] X. Huang, C. Ai, H. Yao, C. Zhao, C. Xiang *et al*., *eFood*, **3**, e37 (2022), https://doi.org/10.1002/efd2.37

[23] Y. Zhu, X. Feng, J. Guo, L. Wang, X. Guo *et al*., *Front. Nutr*., **9**, 1021448 (2022), https://doi.org/10.3389/fnut.2022.1021448

[24] M. T. Haseeb, M. A. Hussain, S. H. Yuk, S. Bashir and M. Nauman, *Carbohyd. Polym*., **136**, 750 (2016), http://dx.doi.org/10.1016/j.carbpol.2015.09.092

[25] G. Muhammad, M. A. Hussain, M. U. Ashraf, M. T. Haseeb, S. Z. Hussain *et al*., *RSC Adv*., **6**, 23310 (2016), https://doi.org/10.1039/C5RA23088H

[26] M. U. Ashraf, M. A. Hussain, G. Muhammad, M. T. Haseeb, S. Bashir *et al*., *Int. J. Biol. Macromol*., **95**, 138 (2017), http://dx.doi.org/10.1016/j.ijbiomac.2016.11.057

[27] B. A. Lodhi, M. A. Hussain, M. Sher, M. T. Haseeb, M. U. Ashraf *et al*., *Adv. Polym. Technol*., **2019**, 9583516 (2019), https://doi.org/10.1155/2019/9583516

[28] M. Farid-ul-Haq, M. A. Hussain, M. T. Haseeb, M. U. Ashraf, S. Z. Hussain *et al*., *RSC Adv*., **10**, 19832 (2020), https://doi.org/10.1039/D0RA03176C

[29] J. Irfan, M. A. Hussain, M. T. Haseeb, A. Ali, M. Farid-ul-Haq *et al*., *RSC Adv*., **11**, 19755 (2021), https://doi.org/10.1039/D1RA02219A

[30] A. Ali, M. A. Hussain, M. T. Haseeb, S. N. A. Bukhari, G. Muhammad *et al*., *Curr. Drug Deliv*., **20**, 292 (2023), https://doi.org/10.2174/1567201819666220509200019

[31] M. Rahimi, G. Charmi, K. Matyjaszewski, X. Banquy and J. Pietrasik, *Acta Biomater*., **123**, 31 (2021), https://doi.org/10.1016/j.actbio.2021.01.003

[32] P. Ghasemiyeh and S. Mohammadi-Samani, *Front. Mater.*, **8**, 752813 (2021), https://doi.org/10.3389/fmats.2021.752813
[33] P. Jana, M. Shyam, S. Singh, V. Jayaprakash and A. Dev, *Eur. Polym. J.*, **142**, 110155 (2021), https://doi.org/10.1016/j.eurpolymj.2020.110155
[34] T. Osmałek, A. Froelich, B. Jadach, A. Tatarek, P. Gadziński *et al.*, *Pharmaceutics*, **13**, 884 (2021), https://doi.org/10.3390/pharmaceutics13060884
[35] F. Sabbagh and B. S. Kim, *J. Control. Release*, **341**, 132 (2022), https://doi.org/10.1016/j.jconrel.2021.11.025
[36] H. Abdelkader, Z. Fathalla, A. Seyfoddin, M. Farahani, T. Thrimawithana *et al.*, *Adv. Drug Deliv. Rev.*, **177**, 113957 (2021), https://doi.org/10.1016/j.addr.2021.113957
[37] A. Koyyada and P. Orsu, *J. Drug Deliv. Sci. Technol.*, **63**, 102431 (2021), https://doi.org/10.1016/j.jddst.2021.102431
[38] M. T. Haseeb, M. A. Hussain, S. Bashir, M. U. Ashraf and N. Ahmad, *Drug Dev. Ind. Pharm.*, **43**, 409 (2017), https://doi.org/10.1080/03639045.2016.1257017
[39] M. U. Ashraf, M. A. Hussain, S. Bashir, M. T. Haseeb and Z. Hussain, *J. Drug. Deliv. Sci. Technol.*, **45**, 455 (2018), https://doi.org/10.1016/j.jddst.2018.04.008
[40] M. S. Bami, M. A. R. Estabragh, P. Khazaeli, M. Ohadi and G. Dehghannoudeh, *J. Drug Deliv. Sci. Technol.*, **70**, 102987 (2022), https://doi.org/10.1016/j.jddst.2021.102987
[41] Y. Mu, L. Gong, T. Peng, J. Yao and Z. Lin, *OpenNano*, **5**, 100031 (2021), https://doi.org/10.1016/j.onano.2021.100031
[42] M. M. Waegele, C. M. Gunathunge, J. Li and X. Li, *J. Chem. Phys.*, **151**, 160902 (2019), https://doi.org/10.1063/1.5124878
[43] M. Rizwan, R. Yahya, A. Hassan, M. Yar, A. D. Azzahari *et al.*, *Polymers*, **9**, 137 (2017), https://doi.org/10.3390/polym9040137
[44] H. Namazi, M. Hasani and M. Yadollahi, *Int. J. Biol. Macromol.*, **126**, 578 (2019), http://dx.doi.org/10.1016/j.ijbiomac.2018.12.242
[45] W. Tanan, J. Panichpakdee and S. Saengsuwan, *Eur. Polym. J.*, **112**, 678 (2019), https://doi.org/10.1016/j.eurpolymj.2018.10.033
[46] M. Pandey, M. C. I. M. Amin, N. Mohamad, N. Ahmad and S. Muda, *Polym-Plast. Technol. Eng.*, **52**, 1510 (2013), https://doi.org/10.1080/03602559.2013.820755
[47] G. Muhammad, M. T. Haseeb, M. A. Hussain, M. U. Ashraf, M. Farid-ul-Haq *et al.*, *Drug Dev. Ind. Pharm.*, **46**, 122 (2020), https://doi.org/10.1080/03639045.2019.1706551
[48] B. A. Lodhi, M. A. Hussain, M. U. Ashraf, M. T. Haseeb, G. Muhammad *et al.*, *Ind. Crop. Prod.*, **155**, 112780 (2020), https://doi.org/10.1016/j.indcrop.2020.112780
[49] M. Farid-ul-Haq, M. T. Haseeb, M. A. Hussain, M. U. Ashraf, M. Naeem-ul-Hassan *et al.*, *J. Drug Deliv. Sci. Technol.*, **58**, 101795 (2020), https://doi.org/10.1016/j.jddst.2020.101795
[50] M. Gibaldi and S. Feldman, *J. Pharm. Sci.*, **56**, 1238 (1967), https://doi.org/10.1002/jps.2600561005
[51] R. W. Korsmeyer, R. Gurny, E. M. Doelker, P. L. Buri and N. A. Peppas, *Int. J. Pharm.*, **15**, 25 (1983), https://doi.org/10.1016/0378-5173(83)90064-9
[52] P. L. Ritger and N. A. Peppas, *J. Control. Release*, **5**, 37 (1987), https://doi.org/10.1016/0168-3659(87)90035-6
[53] J. G. Wagner, *J. Pharm. Sci.*, **58**, 1253 (1969), https://doi.org/10.1002/jps.2600581021
[54] K. Huanbutta, K. Cheewatanakornkool, K. Terada, J. Nunthanid and P. Sriamornsak, *Carbohyd. Polym.*, **97**, 26 (2013), https://doi.org/10.1016/j.carbpol.2013.04.073