Review

Cellulose based polymers in development of amorphous solid dispersions

Rahul B Chavan, Sneha Rathi, Vaskuri G S Sainaga Jyothi, Nalini R Shastri*

Solid State Pharmaceutical Research Group (SSPRG), Department of Pharmaceutics, National Institute of Pharmaceutical Education and Research, Hyderabad 500037, India

A R T I C L E   I N F O

Article history:
Received 4 July 2018
Revised 27 August 2018
Accepted 10 September 2018
Available online 18 October 2018

Keywords:
Supersaturation
HPMC
Amorphous form
Crystallization
Polymers

A B S T R A C T

Cellulose derivatives have gained immense popularity as stabilizers for amorphous solid dispersion owing to their diverse physicochemical properties. More than 20 amorphous solid dispersion-based products that have been approved for marketing consist of cellulose derivatives as stabilizers, thus highlighting their importance in generation of amorphous solid dispersions. These polymers offer numerous advantages like drug solubilization, crystallization inhibition and improvement in release patterns of drugs. Exploring their potential and exploiting their chemistry and pH responsive behaviour have led to the synthesis of new derivatives that has broadened the scope of the use of cellulose derivatives in amorphous formulation development. The present review aims to provide an overview of different mechanisms by which these cellulose derivatives inhibit the crystallization of drugs in the solid state and from supersaturated solution. A summary of different categories of cellulose derivatives along with the newly explored polymers has been provided. A special segment on strengths, weaknesses, opportunities, and threats (SWOT) analysis and critical quality attributes (CQAs) which affect the performance of the cellulose based amorphous solid dispersion will aid the researchers in identifying the major challenges in the development of cellulose based solid dispersion and serve as a guide for further formulation development.

© 2018 Shenyang Pharmaceutical University. Published by Elsevier B.V.
This is an open access article under the CC BY-NC-ND license.
(http://creativecommons.org/licenses/by-nc-nd/4.0/)

1. Introduction

Polymers play a pivotal role in the stabilization of amorphous solid dispersions by retaining the drug in an amorphous form in the polymeric matrix during storage, thereby inhibiting crystallization of the drug in the matrix [1]. Exposure to aqueous media results in rapid drug release from the amorphous solid dispersion, thus generating supersaturation. The rapid release of drug can be attributed to the elimination of energy
required for disruption of the crystal lattice. The resultant supersaturated solution possesses the tendency to desuper-
saturate and attain the stable crystalline form. Stabilization
polymers when used must be effective in inhibiting the
-crystallization of drug from the supersaturated solution for
the duration of transport through the absorptive zones of
the gastrointestinal (GI) tract. According to Fick’s law, absorp-
-tion of a drug across the intestinal epithelial trans mem-
-brane is directly proportional to the achieved supersatura-
tion ratio. Hence, polymer selection for development of amorphous
solid dispersion is of paramount importance. The polymer
must be compatible with the drug and promote drug-polymer
interactions for effective stabilization of the produced system.

Cellulose derivatives have been predominantly used in
the stabilization of amorphous form of drugs. The dominance
of cellulose derivatives as stabilizers is evident from the number
of amorphous solid dispersions [2], that have been approved
by the regulatory authorities for marketing (Table 1). This
remarkable popularity may be attributed to their high
molecular

Table 1 - List of marketed amorphous solid dispersion products containing cellulose derivatives as stabilizers (*product
withdrawn from market).

| Year of approval | Name of the product | API | Polymer used | Company | Technology used | Dosage form |
|------------------|---------------------|-----|--------------|---------|----------------|------------|
| 1989             | Nivadil®            | Nivadipine | HPMC       | Fujisawa Pharmaceutical Co. Ltd | HME | Tablet |
| 1992             | Sporanox®          | Itraconazole | HPMC | Janssen Pharmaceuticals | Fluid bed bead layering | Capsule |
| 1994             | Prograf®            | Tacrolimus | HPMC       | Astellas Pharma Inc. | Spray drying, Fluid bed | Capsule |
| 1997             | Rezulin®             | Troglitazone | PVP/HPMC | Pfizer | – | Tablet |
| 2002             | Crestor®             | Rosuvastatin | HPMC | Astra Zeneca | Spray drying | Tablet |
| 2004             | Cymbalta®            | Duloxetine | HPMCAS | Eli Lilly | – | Capsule |
| 2007             | Eucreas®             | Vildagliptin/ Metformin HCL | HPC | Novartis Pharmaceuticals | HME | Tablet |
| 2008             | Intience®            | Etravirine | HPMC | Janssen Pharmaceuticals | Spray drying | Tablet |
| 2009             | Modgraf®             | Tacrolimus | HPMC | Astellas Pharma Europe B.V. | Spray drying | Granules for oral suspension |
| 2009             | Samgsca®             | Telvaptan | HPMC | Otsuka Pharma | Granulation | Tablet |
| 2010             | Certican® or Zortress® | Everolimus | HPMC | Novartis Pharmaceuticals | Spray drying | Tablet |
| 2010             | Omecl®               | Itraconazole | HPMC | Stiefel | HME | Tablet |
| 2011             | Incivek® (US), Incivo® (EU) | Telaprevir | HPMCAS | Vertex Pharmaceuticals | Spray drying | Tablet |
| 2011             | Zelboraf®            | Vemurafenib | HPMCAS | Roche | Co-precipitation | Tablet |
| 2012             | Kalydeco®            | Ivacaftor | HPMCAS/SLS | Vertex Pharmaceuticals | Spray drying | Tablet |
| 2013             | Astagraf XL®         | Tacrolimus | HPMC | Astellas Pharma Inc. | Wet granulation | Capsule |
| 2013             | Nofaxi®             | Posaconazole | HPMCAS/HPC | Merck | HME | Tablet |
| 2015             | Orkimbel®           | Lumacaftor/ Ivacaftor | HPMCAS/SLS | Vertex Pharmaceuticals | Spray drying | Tablet |
| 2015             | Isoptin- SRL®       | Verapamil | HPC/HPMC | AbbVie Inc. | HME | Tablet |
| 2015             | Envarsus®           | Tacrolimus | Poloxamer/HPC | Veloxis Pharmaceuticals | Melt dose technology | Tablet |
| 2016             | Zepatier®            | Elbasvir/ Grazoprevir | TPGS, Copovidone, and HPMC | Merck | Spray drying | Tablet |

(Tg) make them the best stabilizers for amorphous solid dis-
-persion generation. The strengths, weaknesses, opportunities,
and threats (SWOTs) of cellulose derivatives based amorphous
solid dispersions are depicted in Fig. 1.

Numerous articles shed light on the synthesis, character-
-ization and application of cellulose derivatives in the develop-
-ment of amorphous solid dispersions, [3–7] however, an
-overview on the mechanism by which cellulose derivatives in-
-hibit crystallization both in the solid state and in solution
-post solubilization in the aqueous medium is lacking. Hence, a
-major objective of this review is to provide a comprehensive dis-
-cussion on the role of cellulose derivatives in amorphous sta-
-bilization and maintenance of supersaturation. Additionally,
-a special segment has been provided on the preparation and
- characterization techniques along with the regulatory per-
-spective, delineating the critical quality attributes (CQAs) that
-affect the performance of amorphous solid dispersions.

2. Background of cellulose-based polymers

Cellulose is the most abundant biopolymer in the world,
followed closely by chitin. As the chief structural component
of plants, cellulose is an almost inexhaustible polymeric raw
material with a fascinating structure and properties. Cellulose
has been in use as a raw material for over 150 years. This
polysaccharide consists of a linear chain of a variable length of 1-4-linked β-D-anhydroglucopyranose units (Fig. 2). These repeating units are covalently linked via acetal functions between the equatorial –OH group of C₄ and the C₁ carbon atom.

Cellulose is a highly hydrophilic polymer, having hydrophilic-lipophilic balance (HLB) number at 12.45. However, it is not soluble in water in its native form due to its strong intramolecular and intermolecular hydrogen bonding between the individual chains and a high degree of crystallinity (in the range of 40%–60%). Hence, cellulose is chemically modified to water-soluble cellulose ester or ether derivatives. In cellulose ethers, part of the hydrogen atoms of the three hydroxyl groups on the anhydroglucose repeating unit is replaced by alkyl or mixed alkyl groups (Fig. 2). Such modifications of cellulose via esterification or etherification of the hydroxyl groups are termed as “cellulosics”. The versatile properties of cellulose ethers such as their aqueous solubility, enhanced viscosity, rheology and water retention ability have been utilized for diverse applications [8]. They are well known for their use as suspension stabilizing agents, thickening agents, bonding agents, adhesives, coating compositions, film-forming agents, thermoplastic materials, finishing compositions, emulsion stabilizers, protective colloids and plastic sheets. These varied properties and applications of cellulose ethers have helped them to maintain a strong market presence.

Cellulose derivatives are generally categorized based on their pH-responsive behaviour and chemistry as pH responsive, hydrophilic and hydrophobic cellulose derivatives (Fig. 3 and Table 2). Considering the extensive list of examples under all these categories, our discussion is restricted to the cellulose derivatives which find utility in the development of amorphous solid dispersion (Table 2). Summary of the properties, advantages and limitations of cellulose derivatives which are explored for amorphous solid dispersion development were summarized in Table 2.

2.1 Conventional cellulose esters and ethers

Alkylation of cellulose yields a class of polymers commonly termed as cellulose ethers. Methylcellulose (MC), ethylcellulose (EC), hydroxypropylcellulose (HPC), hydroxyethylcellu-
Fig. 2 – Chemical structure cellulose with two β-1,4 linked anhydroglucose units (A), cellulose ether derivatives (B) and cellulose ester derivatives (C).

Fig. 3 – Classification of cellulose-based polymers.
Table 2 – Cellulose derivatives explored in preparation of amorphous solid dispersions.

| Polymer category                  | Examples                                      | Properties                                      | Advantages                                      | Limitations                                      |
|-----------------------------------|-----------------------------------------------|------------------------------------------------|------------------------------------------------|-------------------------------------------------|
| Conventional cellulose esters and ethers | CHC, HPMC, HPC, EC, MC, CA, CAB, HPC-Pen106-AA-H | Hydrolytically stable, water-insoluble, pH non-responsive | Safe, low moisture absorption ability | Lacks very strong H-bond donor or acceptor groups |
| pH-responsive cellulose esters and ethers | CABSu, HPMCAS                                  | Water insolubility at low pH, amphiphilic, stability of HPMCAS at high temperature and shear, Highly soluble in organic solvent, dissolve at pH 5–7 | Moderate moisture absorption ability, Strong drug-polymer interactions | CABSu hydrolytically unstable, HPMCAS is complex to synthesize and analyze. Synthesis of HPMCAS may be difficult to control due to the potential for variable chain extension of the hydroxypropyl group. Polymer with low DS, insufficient to provide bulk solubility, polymers vulnerable to cross-linking, polymer synthesis Limited miscibility with drugs |
| Carboxymethylcellulose derivatives | CMC, CMCAB                                    | Good organic solvent solubility, Broad miscibility with hydrophobic drugs, pH-sensitive, Swells at neutral pH | Aqueous based coatings applications | — |
| Cellulose phthalate derivatives    | HPMCP, GAPth                             | Dissolves at 5 pH (more than 6) | More rigid cellulose polymer backbone sterically hinder recrystallization of drug and improve the stability of the system | — |
| Cellulose ω-carboxy esters        | CA AdP, CA Sub, MCAd, CAB Seb, CAP Sub, CAP Seb, CAB Sub, CA Seb | High T_g, More hydrophobic, Amphiphilic nature | Good solubility in medium polar solvent, Broader miscibility with water | Cross-linking potential during synthesis |

Keywords: CAAdP- Cellulose acetate adipate propionate; CAPth- Cellulose acetate phthalate; CA Sub- Cellulose acetate suberate; CA Adp- Cellulose acetate adipate; CA Seb- Cellulose acetate sebacate; CHC- 5-carboxypentyl hydroxypropyl cellulose; CMC- Carboxymethyl cellulose; CMcAB- Carboxymethyl cellulose acetate butyrate; EC- Ethylcellulose; HEC-Hydroxyethyl cellulose; HPC- Hydroxypropyl cellulose; HPC-Pen106-AA-H- Hydroxypropyl pent-4- enyl cellulose; HPMC- Hydroxypropylmethyl cellulose; HPMCAS- Hydroxypropylmethylcellulose acetyl succinate; HPMCP- Hydroxypropylmethyl cellulose phthalate

lose (HEC), and hydroxypropylmethylcellulose (HPMC) are the most widely used cellulose ethers in pharmaceutical industry. Cellulose esters and ethers are of particular interest for developing amorphous solid dispersions because of their physicochemical properties such as high molecular weight and resistance to hydrolysis which prevents the absorption of most cellulose ethers and esters in the GI tract. Even under extreme circumstances, if a small degree of hydrolysis were to occur through chemical or lipase-catalyzed hydrolysis, the resulting by-products (cellulose, glucose and carboxylic acids) would be endogenous or dietary. Amongst the cellulose derivatives, cellulose ethers are relatively hydrolytically stable, and remain unalloyed under GI conditions that proves advantageous in oral drug delivery systems [9,10].

HPMC is the most commonly explored cellulose derivative for generation of amorphous solid dispersion. This water-soluble cellulose ether is not pH-responsive and lacks very strong hydrogen bond donor and acceptor groups. Although HPMC lacks the ability to form strong intermolecular interactions, it has been effectively used in the formulation development of amorphous solid dispersions, which can be gauged from its presence in more than fifty percent of the marketed amorphous solid dispersion products (Table 1).

2.2. pH-responsive cellulose esters and ethers

In recent times, many cellulose derivatives have been explored for the development of amorphous solid dispersions with a special objective to devise pH-responsive release of drugs. Cellulose polymers containing carboxyl groups, remain unionized at the acidic pH, and prevent drug release in the gastric region. Rigid cellulosic polymer backbones, as in the case of cellulose phthalate and derivatives sterically hinder drug recrystallization and help in maintenance of supersaturation [10]. Polymers may be structurally modified to enable triggered drug release and enhance the affinity for drugs through specific interactions. Cellulose is inherently hydrophilic, and a low degree of substitution (DS) of nearly any substituent including non-polar ones, can disrupt the H-bonding and thereby impart water solubility. A typical polymer chain of this class contains an amphiphilic cellulose derivative with pendant carboxylic acids to achieve pH-triggered swelling and drug release. These polar pendant groups also help in the formation of energetically favourable specific molecular interactions. Various pH-responsive cellulose lose esters and ethers which have been explored for development of amorphous solid dispersions are discussed be-
low along with the potential advantages over other cellulose ethers and esters.

2.2.1. Cellulose succinate
Eastman Chemical Company first reported the amphiphilic, water-dispersible cellulose succinate mixed esters. HPMCAS is the most extensively studied polymer under this category for formulation development as an amorphous solid dispersion matrix polymer. The capability of producing effective and stable amorphous solid dispersions is demonstrated by more than five HPMCAS containing products approved for marketing by the regulatory authorities. Similarly, research at Pfizer Inc. and Bend Research reported at least 1.5-fold solution concentration enhancement of ziprasidone hydrochloride by merely mixing drug with HPMCAS in solution [11]. In another study, Kennedy et al., reported nearly 28-fold enhancement in the dissolution rate of a highly selective VR1 antagonist (AMG 517) from an amorphous solid dispersion with HPMCAS compared to crystalline drug, and a nearly 2-fold improvement compared to amorphous drug [12]. HPMCAS has proved to be a highly effective polymer in a solid dispersion with nifedipine [3]. Primarily, the amount of polymer required for generation of amorphous solid dispersion was less than that required for methacrylic acid-ethyl acrylate copolymer or PVP. Relatively less tendency to absorb moisture over PVP and PEG add to the advantages of using HPMCAS above the other two in the development of amorphous solid dispersion [12]. Yin et al., synthesized five HPMC esters using mono-substituted succinic anhydrides and evaluated these synthesized polymers for generation and maintenance of supersaturated solution of phenytoin for longer duration from spray dried dispersions. These new HPMC succinates showed superiority over HPMCAS for maintenance of supersaturation for longer duration mainly due to nucleation inhibition [13].

2.2.2. Carboxymethylcellulose derivatives
CMC is an anionic, water-soluble cellulose ether, which is usually manufactured in large quantities through etherification of activated alkali cellulose with chloroacetic acid [14]. Allen and co-workers synthesized these CMC mixed esters with various DS (alkanoates), based on the feed ratios and reaction conditions. The commercially produced CMCC polymers contain DS (CMC) of 0.29–0.35, DS (butyryl) of 1.37–1.64 and DS (Ac) of 0.30–0.55 [10]. For miscible, poorly water-soluble drug such as fexofenadine HCl, amorphous solid dispersion was generated using CMCC polymer matrix using intimate mixing [15]. This amorphous blend of fexofenadine HCl in CMCC led to a sharp enhancement of solubility of drug along with sufficient solution stability (little or no crystallization over time).

2.2.3. Cellulose phthalate derivatives
Malm et al., identified CAPth as a pH-sensitive coating polymer [16]. CAPth is well-suited to this application as it is soluble in organic solvents and acts as a good film former. Due to its ionization at relatively low pH, CAPth has been explored as a matrix for amorphous dispersions. In vivo testing conducted in Sprague Dawley rats demonstrated a significant two-fold enhancement in oral bioavailability from a CAPthitraconazole amorphous solid dispersion compared to Sporanox®, the marketed dosage form of itraconazole. Structural features of CAPth, like rigid cellosic polymer backbone, led to improved stabilization of the drug in amorphous solid dispersions as compared to those formulated using PVAP [17]. However, the cellulose phthalate derivatives have not yet been exploited to their full potential in development of stable amorphous solid dispersions due to challenges like limited miscibility with the drug molecules and thus, only a few reports have come to light so far [10].

2.2.4. Cellulose ω-carboxy esters
Cellulose alkyl ethers can be successfully esterified with ω-carboxyalkanoyl groups by reaction with monobenzyl adipoyl, suberoyl, and sebacoyl chlorides, and subsequent benzyl ester hydrogenolysis, to avoid cross linking. The resultant cellulose ester products are more hydrophobic than the starting ethers, and thus have good solubility in medium polarity solvents, and in polar aprotic solvents. The ethyl cellulose esters have broader organic solubility, ascribed to their higher DS(alkyl) and the relatively higher hydrophobicity of the ethyl group as compared to the methyl group [18]. This organic solubility aids in the formation of amorphous solid dispersions from common solutions of drug and polymer, and is also predictive of broad miscibility with drug structures [19]. The alkyl cellulose ω-carboxyalkanoates have shown favorable drug release patterns and stabilization of the drug against recrystallization after release from amorphous solid dispersion [19]. This chemistry promises to make available a very broad range of alkyl cellulose ω-carboxyalkanoates which can be tailored to achieve the desired outcome in developing amorphous solid dispersions. The promising nature of these renewable amphiphiles for solubility and bioavailability enhancement of otherwise poorly soluble drugs is underlined by successful formation of an amorphous solid dispersion of ritonavir [4]. Similar results have been reported for other drugs (Table 3).

3. General mechanisms behind amorphous state stabilization and crystallization inhibition

In amorphous solid dispersion, drug is kinetically entrapped between the polymer chains in a high energy non-crystalline state leading to improved stability [20–23]. Extensive literature is available on the mechanisms of by which polymer stabilizes amorphous drug or glass solution of the drug in a glassy polymer matrix. Interested readers are encouraged to refer to the excellent reviews [20,24,25]. Some of the prominent mechanism by which polymers prevent crystallization of amorphous drug are described in Fig. 4, which includes reduction of the drug molecular mobility, increasing the glass transition temperature, $T_g$ (anti plasticization effect), and/or through molecular interaction with the drug [25]. Polymers may prevent the precipitation of the drug from supersaturated solution by increasing the viscosity of the medium which help in reduction of nucleation rate by reducing the molecular mobility. In addition, this impairs the crystal growth by affecting diffusion coefficient which is directly proportional to the crystal growth rate [26]. Polymers may also get adsorbed onto
Table 3 – Examples of cellulose-based polymers explored for amorphous solid dispersion development.

| Year   | Drug        | Polymers                          | Characterization       | Observations                                                                 | Ref No. |
|--------|-------------|-----------------------------------|------------------------|------------------------------------------------------------------------------|---------|
| 2006   | Felodipine  | PVP, HPMCAS and HPMC              | HSM                    | Effect of polymers on nucleation rate and impact of drug-polymer interactions was studied | [50]    |
| 2011   | Indomethacin| HPMC, PVP and HP-β-CD             | Second derivative UV–Vis spectrometry | Description of crystal growth kinetics modelling                             | [51]    |
| 2012   | Ritonavir   | HPMC and new derivatives of Cellulose ω-carboxy esters HPMC | UV–Vis spectrometry   | Polymer efficiency in inhibiting crystal growth decreased at lower pH and higher supersaturation conditions | [27]    |
| 2012   | Felodipine  | HPMC                              | Population balance equation | HPMC was more effective in inhibiting nucleation than growth rate              | [5]     |
| 2013   | Naringenin  | CAAAdP, HPMCAS, CMCAB             | UV–Vis spectrometry    | The carboxylated cellulose esters were effective in stabilizing the solution in supersaturated condition | [52]    |
| 2013   | Curcumin    | CAAAdP, HPMCAS, CMCAB             |                        | The hydrophobicity of CMCAB and CAAAdP aided in stabilizing the system against crystallization in 6.8 pH buffer solution | [43]    |
| 2013   | Efavirenz, Ritonavir, Celecoxib | HPMC, HPMCAS, new derivatives of Cellulose ω-carboxy esters | UV–Vis spectrometry | HPMC was effective in inhibiting nucleation than crystal growth | [30]    |
| 2013   | Danazol, griseofulvin | HPMC, PVP, Eudragit E-100 |                        | The ionization extent of carboxylic acid substituent of cellulose-based polymers showed effect on drug-polymer interactions and thus on the growth rate | [42]    |
| 2013   | Quercetin   | HPMCAS, CAAAdP, CMCAB             |                        | Precipitation inhibitory efficiency of polymers followed the order HPMC > PVP > > Eudragit | [53]    |
| 2013   | Ellagic acid| HPMCAS, CAAAdP, CMCAB             |                        | Crystallization inhibitory potential followed the order HPMCAS > CMCAB > CAAAdP | [42]    |
| 2013   | Indomethacin| HPMC, PVP and HP-β-CD             | Second derivative UV–Vis spectrometry | Impact of degree of supersaturation on kinetics of crystal growth was demonstrated | [55]    |
| 2014   | Danazol     | HPMC, HPMCAS                       | UV and fluorescence spectroscopy | HPMC and HPMCAS decreased the supersaturation and thus lowered the nucleation rate | [37]    |
| 2014   | Ritonavir   | New derivatives of Cellulose ω-carboxy esters | UV–Vis spectrometry | Moderately hydrophobic cellulose-based polymers with substituent of high ionizable carboxylic acids were better inhibitors of crystallization | [19]    |
| 2014   | Acetaminophen| PVP K-12, PVPVA, HPMC, HPMCAS, PAA |                        | In solution: Inhibition of only primary nucleation: PVP, PVPVA > HPMC > HPMCAS > PAA; Inhibition of both primary and secondary nucleation: PVP > HPMC > HPMCAS > PVPVA > PAA; In solid state: PAA > PVP > PVPVA > HPMC > HPMCAS | [56]    |
| 2015   | Felodipine  | HPMCAS, HPMC, PVP, PAA, PVPVA, P2VP, PVAc | UV–Vis spectrometry | A linear relationship between polymer surface coverage and polymer effectiveness as a growth rate inhibitor and a model based on Kubota-Mullin model was developed for the same HPMC and HPMCAS inhibited nucleation induction time for more than 8 h. PVP was a poor nucleation inhibitor. | [34]    |
| 2015   | Celecoxib   | PVP K-12, PVP K 29/32, HPMCAS, HPMC 606 |                        |                                                                              | [38]    |

(continued on next page)
Table 3 (continued)

| Year | Drug          | Polymers                  | Characterization                  | Observations                                                                                                                                                                                                 | Ref No. |
|------|---------------|---------------------------|-----------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|
| 2015 | Felodipine    | HPMCAS                    | Rotating disk apparatus with a UV probe | HPMCAS was adsorbed on the active sites at the solid-liquid interface and slowed down the crystal growth by preventing attaching of growth units to the crystal.                                                                 | [35]    |
| 2016 | Telaprevir    | Carboxy-terminal cellulose ether esters | UV-Vis spectrometry               | More hydrophilic derivatives of cellulose ether had good hydrophilic/hydrophobic balance promoting aqueous solubility and interactions with drug.                                                               | [57]    |
| 2016 | Felodipine    | HPMCAS                    | UV-Vis spectrometry               | HPMCAS effectively reduced the growth steps, was relatively more efficacious when the surface was pre-poisoned with HPMCAS.                                                                                      | [36]    |
| 2016 | Celecoxib     | HPMC 606, HPMCAS AS-MF    | Dissolution study                 | HPMC, HPMCAS were effective in inhibiting crystallization, however, were required in combination with a third miscible polymer to improve the dissolution characteristics.                                              | [7]     |
| 2016 | Danazol       | PVP K29/32, HPMC 606, HPMCAS (AS-MF) | UV-Vis spectrometry               | In the absence of polymers, drug crystallized within 10–15 min, while in the presence of the polymers induction time was increased from 30 min to 6 h depending on the polymer. HPMCAS showed highest precipitation inhibitory potential than PVP and HPMC. | [58]    |
| 2016 | Telaprevir    | HPC, HPMCAS, HPC-Pen106-AA-H | UV-Vis spectrometry               | With all three polymers, induction time increased by 8-fold. HPC did not effectively prevent amorphous particle growth, whereas the carboxyl-containing HPC-Pen106-AA-H and HPMCAS were able to prevent formation of agglomerates of amorphous drugs | [59]    |
| 2016 | Nifedipine    | HPMC, HPC, and PVP        | UV-Vis spectrometry               | HPMC inhibited both nucleation and crystal growth, and showed highest supersaturation holding capacity.                                                                                                     | [31]    |
| 2017 | Ritonavir     | MC, EC, adipate, sebacate, suberate of the ethyl and methyl ethers | Dissolution study                 | Release of ritonavir was rapid and recrystallization was prevented for a time period equivalent to the probable duration of passage through the absorptive zone of the GI tract.                                        | [4]     |
| 2017 | Quercetin     | HPMCAS, PVP, CCAB, CASub  | PXRD, SEM                        | Compared to HPMCAS, CASub provided stable and high supersaturation. Combining PVP into CCAB and CASub amorphous solid dispersions was effective and provided high drug release and stable supersaturation.                        | [60]    |
| 2017 | Indomethacin  | HPMC, Eudragit EPO        | UV–Vis and fluorescence spectroscopy, DLS, dissolution study | Improved dissolution profiles with ternary amorphous solid dispersion of indomethacin with EPO and HPMC due to ionization of EPO at acidic pH, leading to rapid drug release with a nano-droplet formation, and effective crystallization inhibition by HPMC. | [61]    |
| 2017 | Rifampin      | CMCAB, CAAdP, CABSb       | Dissolution study                 | All the polymers were effective in increasing the drug release and preventing recrystallization, thus increasing stability of the drug at the different pH conditions.                                                                 | [6]     |
| 2018 | Rifapentine   | HPMCAS, CASub, and CHC    | Dissolution study                 | Polymers improved the stability of drug in gastric pH                                                                                                                                                       | [62]    |
Table 3 (continued)

| Year | Drug | Polymers | Characterization | Observations | Ref No. |
|------|------|----------|------------------|--------------|---------|
| 2018 | Griseofulvin | HPMC and MC | Solvent shift method using UV fiber optic detection system | Two key parameters—similarity in hydrophobicity between drug and polymer and presence of hydroxypropyl groups in the cellulosic polymer for hydrogen bonding contributed significantly to the precipitation inhibitory potential of cellulose polymers | [63] |
|      |       |          |                  |              |         |
| 2008 | Felodipine | HPMC, HPMCAS and PVP | Dissolution study | HPMC and HPMCAS were superior to PVP in amorphous stabilization and precipitation inhibition of felodipine | [64] |
| 2010 | Felodipine, indomethacin | PVP K 29/32, HPMC 606, HPMCAS AS-MF | PXRD, Raman spectroscopy | Crystallization inhibition of indomethacin and felodipine by PVP, HPMC, and HPMCAS | [65] |
| 2011 | Many drug molecules | HPMC, HPMCAS | PLM | HPMC and HPMCAS are moderate strength acceptors and strong donors and inhibited crystallization of drugs containing hydrogen bond acceptor groups | [66] |
| 2012 | Acetaminophen | HPMC, HPMCAS | HSM, DSC | Both polymers effectively inhibited nucleation than crystal growth rate | [67] |
| 2014 | Nifedipine | HPMC, HPMCAS | Raman spectroscopy | Not effective in inhibiting the crystallization of amorphous form | [68] |
| 2014 | Papaverine HCl, dipyridamole, glyburide, warfarin | HPMC, HPMCAS, CMCAB | Wide angle X-ray scattering, PLM | No polymer was effective in inhibition of crystallization of dipyridamole and papaverine. Whereas glyburide and warfarin crystallization was prevented by HPMC. Other polymers slightly delayed the process. | [69] |
| 2014 | Griseofulvin, felodipine, and ketoconazole | PVP-VA and HPMC-AS | Flory-Huggins parameter | Importance of drug-polymer interactions in amorphous stabilization and supersaturation maintenance was demonstrated | [70] |
| 2014 | Felodipine | HPC-SSL and PVP-VA | DSC, PXRD and FTIR | Impact of molecular level dispersion and drug polymer interactions on phase separation was evaluated | [71] |
| 2015 | Felodipine, Nifedipine, Cinnidipine, Nimodipine, Nisoldipine, Nitrendipine | HPMC 606, HPMCAS, PAA, PVP K29/32, PVPVA, CMCAB, CAPAdp | PXRD, H-NMR, PLM, DSC | Crystallization inhibitory potential rank order: PVPVA=HPMC=HPMCAS>PVP > CMCAB=CAPAdp>P2VP=PAA | [72] |
| 2015 | (R and S form of 2-amino-1,1, 3-triphenyl-1-propanol (ATP)) | HPMC, HPMCAS | HSM | HPMC did not show variation in crystal growth inhibition of enantiomers of drug whereas HPMCAS showed variation due to presence of interacting carbonyl groups that were in close proximity to the backbone of cellulose | [73] |
| 2015 | Resveratrol | PVP K 29/32, HPMC 606, HPMCAS (AS-MF), CMCAB, Eudragit E100 | Crystallization kinetics studied using Raman spectroscopy | In comparison to cellulosic polymers, PVP and Eudragit E100 formed strong interactions with drug, effectively preventing recrystallization of the drug from the amorphous complex. | [74] |
| 2016 | Clofazamine | HPMC (HP-55) | ssNMR with quantum chemistry | ssNMR analysis with quantum chemistry calculations confirmed the role of molecular interactions and the critical bonding structure in clofazamine–HPMCP amorphous dispersions stabilizing and improving drug loading capacity | [49] |

(continued on next page)
Table 3 (continued)

| Year | Drug               | Polymers             | Characterization         | Observations                                                                                      | Ref No. |
|------|--------------------|----------------------|--------------------------|---------------------------------------------------------------------------------------------------|---------|
| 2017 | Itraconazole       | HPMCAS- HF, PVPVA64  | PLM, SCXRD, PXRD, Viscosity measurements | Analysis of the itraconazole crystal growth kinetics by the two-dimensional surface nucleation model suggests that the polymers inhibit the crystallization of itraconazole from amorphous dispersions by reducing the molecular mobility in the supercooled liquid and also by elevating the crystal–melt interfacial free energy. | [75]    |
| 2017 | Nifedipine         | HPMCA and HPMCAS    | H-NMR, cryo TEM          | Using H-NMR, polymer distribution in drug rich phase was monitored. Hydrophobicity of the HPMC was responsible behind the phase separation. | [76]    |
| 2018 | Nifedipine         | HPMC                 | MDSC, PXRD, FTIR         | Molecular level dispersion of drug in HPMC polymer helped in improving the apparent solubility and dissolution of nifedipine from amorphous solid dispersion | [77]    |
| 2018 | Naproxen and acetaminophen | HPMCAS, PVP and PVPVA64 | DSC                      | Physical stability of the API/polymer blend was predicted using Kwei equation | [78]    |
| 2018 | Curcumin           | HPMC E5 and Eudragit E100 | In situ Raman spectroscopy | Formation of hydrogen bond between HPMC with curcumin helped in improving the amorphous stabilization | [79]    |

Fig. 4 – Mechanism behind amorphous state stabilization and prevention of precipitation from supersaturated solution by polymers.

the interfacial layer of critical clusters and the reduce crystal growth rate. They alter molecule integration in crystal lattice by changing level of solvation at the crystal medium interface [27]. Similarly, few reports have proposed that reduction of nucleation rate by increasing cluster-medium interfacial energy and reduction in degree of supersaturation by enhancing the solubility of drug affects nucleation and crystal growth [28,29].
4. Role of cellulose derived polymers in amorphous solid dispersion formation and stabilization

4.1. As precipitation inhibitors

Inhibition of crystallization/precipitation of the drug is crucial in drug delivery that are based on supersaturated delivery systems. The gravity of this problem increases with regards to the amorphous systems. Apart from solid-state stability issues, an efficient amorphous dispersion must also address the problems of drug precipitation in the solution state. Prevention of crystallization and maintenance of supersaturated solution for a biologically relevant time frame in GI tract is an essential requirement for sufficient permeation to occur thereby increasing the oral bioavailability. Well-crafted cellulose polymers can not only can prevent crystallization in the solid state, but also prolong supersaturation after amorphous solid dispersions are dispersed in the aqueous medium of the GI tract.

HPMC is one of the most extensively explored cellulose polymers as a precipitation inhibitor and has proven to be effective in stabilizing solid dispersion formulations of many drugs. A list of these solid dispersions is presented in Table 3, along with the methodology utilized for monitoring the precipitation inhibitory potential of the polymers. HPMC is a very versatile polymer and its extensive use can be attributed to the lack of drug specificity. An attempt to explain the mechanism by which HPMC stabilizes the supersaturated systems was made by Alonzo et al. They demonstrated that in presence of HPMC, nucleation and crystal growth rate of felodipine reduced significantly. However, the authors additionally emphasized that the impact of HPMC was more pronounced on nucleation than on crystal growth [5]. To obtain further insight into the mechanism, Kaoutar Abbou Oucherif et al., used population balance modeling for quantitative analysis of the inhibitory effect of HPMC on nucleation and crystal growth rate. The authors’ findings were similar to Alonzo et al., that HPMC has more profound inhibitory activity against nucleation than crystal growth. Additionally, it was also observed that the polymer adsorbed on the crystal surface and slowed down the growth kinetics [30]. In both studies, quantification of the inhibitory effect of HPMC on nucleation was carried out by calculating nucleation induction time in presence and absence of polymer. Findings from our lab when studying the impact of HPMC properties on nucleation and crystal growth inhibition of nifedipine from supersaturated solutions were in line with the previous reports. However, HPMC properties like viscosity, hydrogen bond donor/acceptor and drug solubility were found to influence/impact the inhibitory potential of polymer on nucleation or crystal growth [31].

HPMCAS, a pH-responsive derivative of HPMC is being explored, of late, to stabilize amorphous solid dispersions. This cellulose polymer possesses four types of substituents which are semi-randomly substituted on the hydroxyl groups (bracketed values represent mass content): methoxy (12%–28%, w/w); hydroxypropyl (4%–23%, w/w); acetate (2%–16%, w/w); and succinate (4%–28%, w/w) [32]. Due to the succinate groups, HPMCAS have a pKa of about 5 [33]; therefore, below pH 4, 10% of the polymer ionizes while at least 50% are ionized at pH above 5. The pH-dependent solubility can be attributed to the ratio of succinate and acetyl groups. Thus, different grades of HPMCAS have different pH-dependent solubility (The L, M, and H grades dissolve at pH ≥ 5.5, 6.0 and 6.5, respectively). Presence of hydrophobic methoxy and acetic acid substituents make HPMCAS water-insoluble when unionized (about pH < 5) and remains predominantly colloidal at intestinal pH (i.e. pH 6.0-7.5) [32]. As mentioned earlier, HPMCAS possesses many substituents (methoxy and acetate) which make it relatively hydrophobic. This ultimately results into poor solubility of polymer even when it is ionized in small intestinal pH and leads to the formation of colloidal polymer aggregates in aqueous solutions. The hydrophobic nature of the substituents combined with the colloidal nature of HPMCAS promote interactions between the polymer and insoluble drug molecules, resulting in the formation of amorphous drug/polymer nanostructures in solution. In addition, the negatively charged succinate groups keep these nanostructures stable, evading the large hydrophobic aggregates of the polymer and drug in solution. These drug/polymer nanostructures constitute a high-energy (high-solubility) form of amorphous drug that is stable for several hours to permit GI absorption. Few in vitro measurement studies reported that the nanostructured drug rapidly dissolves to produce a high free-drug concentration that is supersaturated relative to the solution generated by the crystalline drug. From a comparative analysis of the cellulose polymers (Table 2), it can be inferred that HPMCAS has properties conducive to develop stable amorphous systems over its counterparts. Schram et al., investigated the impact of change in polymer conformation as a function of pH on the rate of crystal growth using felodipine and HPMCAS. Effectiveness of the polymer was measured as the ratio of growth rate in the absence and presence of polymer. The study was performed at two different pH conditions such that the polymer remains unionized in one and ionized at the other. The outcome of the study revealed that the polymer was effective at both pH, but the effectiveness dropped by a factor of 1.8 when the polymer was unionized. Intramolecular interactions in the unionized polymer lead to coiling of the chains and are present as globules on the surface of the growing crystal, which increase the exposure of growth sites on the surface of the growing crystals to drug molecules, thus reducing the efficiency of the polymer. HPMCAS with moderate hydrophobicity are adsorbed with highest degree of surface coverage and inhibit crystal growth process significantly, while hydrophilic polymers like PVP and PAA may show little impact on crystal growth [34]. In addition, the polymer surface coverage can be correlated to the polymer effectiveness as a crystal growth inhibitor, using Kubota-Mullin model [35]. In a further study, Schram et al., demonstrated the effectiveness of HPMCAS in inhibiting the crystal growth steps, and reported a higher efficiency when the surface of the crystal was pre-poisoned with the polymer. In growth rate measurements, absence of the polymer from the supersaturated solution led to the development of a drug layer on the pre-poisoned surface. In amorphous solid dispersions, where the drug is dispersed in the polymer matrix, the crystals formed were found to have smaller macroscopic features due to intimate interaction between the drug and the polymer [36]. Addi-
tionally, Schram et al., also demonstrated the impact of structural conformation of HPMCAS on the crystal growth inhibition of felodipine. At a pH higher than the pKa of the polymer, the polymer chains uncoiled and led to efficacious covering of growth sites on felodipine, thus resulting in efficient inhibition of crystal growth. However, the impact was lowered at the pH below the pKa of the polymer due to the coiling of its chains resulting in formation of compacts that were inef-fectively adsorbed onto the surface of the drug, thus exposing the crystal growth sites for adsorption of more growth units [37].

Xie et al., evaluated the impact of polymers on the crystallization propensity of celecoxib in pure amorphous form and also the impact on the dissolution rate from amorphous solid dispersions. PVP was found to be least effective, wherein the nucleation commenced within 60 min, whereas, HPMC and HPMCAS effectively inhibited the crystallization, as no nucleation or crystal growth was observed during the 6 h of the experiment. During the dissolution studies, dispersions with PVP showed tendency to undergo quick/immediate desuper-saturation, while addition of cellulosic polymers reduced the rate of dissolution. The higher efficiency of the cellulosic polymers to inhibit the crystallization of the lipophilic molecule is due to their amphiphilic nature. PVP is relatively hydrophilic and thus interacts with the liquid phase as well. Meanwhile, the cellulosic polymers have greater ability to interact with the drug molecules and thereby effectively block the growth sites [38]. Ueda et al., tried to compare the inhibitory potential of two different grades of HPMCAS (LF and HF) on recrystal-lization of carbamazepine from supersaturated solution using nuclear magnetic resonance spectroscopy. The HF grade was more efficacious in inhibiting the recrystallization of carba-mazepine than the LF grade, which is attributed to stronger intermolecular interactions between the drug and the polymer and higher suppression of molecular mobility of the former over the LF grade [39]. HPMC is available in three substitution grades, namely L, M, H based on the content of the acetyl and succinyl groups. Further each grade is available in two forms based on the particle sizes, fine (F) and granular (G). In an another interesting study, Ricarte et al. using light scattering demonstrated that HPMCAS enhanced the aqueous solu-bility of phenytion and probucol through a formation of ~10 and ~100 nm sized structures in the media [40]. In a similar study, Huang et al., stated that hydroxypropyl acetyl group is the most effective functional group for supersaturation main-tenance, followed by the acetyl group, while the deprotonated succinyl group is the least effective functional group [41].

Numerous ω-Carboxyester derivatives of cellulose such as CAAdP and CASub are a novel class of cellulose es-ter derivatives that have been designed keeping in mind the prerequisites for a polymeric precipitation inhibitor for amorphous solid dispersions. CAAdp and CABSbe are effective in inhibiting crystallization of rifampin [6]. Ilevbare et al., studied the relative ability of structurally diverse cellulose ω-carboxyesters to stabilize lipophilic drugs (cele-coxib, efavirenz, and ritonavir) in solution against nucleation [28] and crystal growth [42]. It has been speculated that the polymer disrupts the reorganization of a cluster of solute molecules into an ordered crystal structure and averts the crystal growth process on the surface of the generated drug crystal. Polymer-solute interactive forces were found to be a major factor behind crystal growth inhibition. The polymers with effective inhibitory potential possess an optimal level of hydrophobicity relative to that of drug molecules and the capability to undergo specific intermolecular interactions, mostly provided by a high number of ionized carboxylate groups (COO−) at pH values reflecting the intestinal environ-ment. Li et al., demonstrated through a structure property study that both the hydrophobicity and carboxyl group content of the polymer significantly contributed in inhibiting the crystallization of ritonavir, specifically crystal growth inhibi-tion, which was found to be highly sensitive to these param-eters [43].

Ilevbare et al., investigated the reason behind crystal growth inhibition of ritonavir by novel cellulose adipec poly-mers at higher pHs [27]. The reduced inhibitory effect of these polymers at low pH was not due to poor carrier adsorption on the ritonavir crystals for inhibiting their growth since a high amount of polymer got adsorbed on the crystals, but rather the polymer conformation at the solid-liquid interface that was found to be the critical factor in the crystal growth inhibition. At low pH, the poorly ionized polymers interacted poorly with the aqueous solvent and resulted into a more condensed con-formation, making them less efficient in holistically covering the ritonavir crystal surface. In contrast, at high pH, the poly-mer chains got extended due to their higher degree of hydration and upon adsorption on the drug crystals, the extended polymer chains blocked more crystal growth sites and ulti-mately inhibited the crystallization process more effectively [27].

Ren, et al., demonstrated that interactions of polymer with drug played important role in prevention of crystalliza-tion from supersaturated solution. Author developed novel microscope-observation method for use following antisolvent recrystallization to evaluate polymers for their ability to in-hibit drug crystallization [44]. Other examples of cellulose derivatives being used as stabilizers in amorphous solid dis-persions are described in Table 3.

4.2. Role in amorphous state stabilization

Formulating poorly water-soluble drugs into amorphous form enhances the solubility. However, highly energetic, pure amorphous products are difficult to scale up as they may rapidly convert into a stable crystalline form by loss of free energy. Moreover, the tendency to recrystallize is exacerbated in presence of water. Zafirlukast (Accolate®, Astra Zeneca), quinapril hydrochloride (Accupril®, Pfizer) and cefuroxime axetil (Ceftin®, GlaxoSmithKline) are the very few commercially available pure amorphous drugs [45]. The amorphous form of the drug may be stabilized thermodynamically or kinetically by formulating as polymeric amorphous solid disper-sions. However, amorphous solid dispersions face challenges of phase separation during their storage due to higher molec-ular mobility in the amorphous state and the tendency to re-crystallize to a lower energy, stable crystalline form [46]. The tendency of the drug to recrystallize must be carefully moni-tored and evaluated during all processing, storage and handling stages in the manufacturing of the drug product [47]. If crystallization occurs, the enhancement in bioavailability
will be negated. Cellulose derivatives are a prominent category of polymers which provide solutions to the above-mentioned challenges of amorphous systems. High $T_g$ values limiting the drug mobility in amorphous solid dispersion, reduction in phase separation due to strong drug-polymer interactions and less moisture adsorbing tendency make cellulose derivatives superior to synthetic polymers like PVA and Eudragits. Numerous mechanisms have been proposed related to specific cellulose derivatives for stabilization of amorphous form of the drug through amorphous solid dispersions. An overview of the few reported studies is provided below.

Konno et al., compared the crystallization inhibitory potential of cellulose derivatives like HPMC and HPMCAS with PVP, on molecularly dispersed amorphous felodipine. It was reported that in the absence of moisture, all three polymers inhibited the nucleation of the drug with the same effectiveness in the amorphous solid dispersions, whereas HPMC and HPMCAS were found to be superior over PVP in crystallization inhibition of felodipine when exposed to atmospheric moisture [1]. Rumornor et al., demonstrated that under 75% RH storage condition, felodipine amorphous solid dispersion containing HPMCAS showed the least moisture adsorption and was resistant to moisture induced drug-polymer immiscibility and recrystallization as compared to PVP. In HPMCAS containing amorphous solid dispersion, crystal growth rate of felodipine was less sensitive to moisture as this polymer possesses numerous hydrogen bond acceptors and donors per repeating unit which can interact with absorbed moisture and resist the disruption of drug-carrier hydrogen bonding [48].

Cellulose phthalate derivatives are a prominent category of cellulose polymers which have shown benefits in the stabilization of amorphous solid dispersions via strong intermolecular interactions. For example, Nie et al., showed the potential of CAPth in amorphous state stabilization of clofazamine through strong interactions using solid state spectroscopic techniques. Due to its ionization at relatively low pH, CAPth has been explored as a matrix for amorphous dispersions [49]. Liu et al., group developed cellulose esters containing adipate as polymer matrices for amorphous solid dispersion. It was proposed that the presence of tetramethylene side chains in adipate groups accentuated the already hydrophobic nature of the cellulose esters, thus aiding in enhancing the miscibility of hydrophobic drugs in polymer, enabling slow drug release. Additionally, the polymer enhanced the miscibility and stability of amorphous solid dispersion through specific interactions between its terminal carboxyl group and hydrogen bond acceptors of the drug [19]. Li et al., in further studies demonstrated through structure property study that the strongly hydrophobic nature of these cellulose-ω-carboxyesters had contributed significantly to crystal growth inhibition in solid state, consequently improving the miscibility of polymer with a hydrophobic drug [42].

5. Regulatory overview of cellulose-based amorphous solid dispersion

Amorphous systems are inherently metastable or thermodynamically unstable due to lack of long-range order, unlike their crystalline counterparts. The amorphous systems have a propensity to revert back to their stable crystalline form, which will eventually hamper the performance of the amorphous solid dispersion. Moreover, the carriers used in amorphous solid dispersions can absorb moisture and catalyze the process of devitrification. Though a product may meet the specifications at the time of approval, it may fail at a later stage leading to batch recalls. Thus, it is essential that the target product is understood holistically to design a robust manufacturing process. It is thereby recommended to abide by the Quality by Design (QbD) framework which is strongly advocated by the US FDA. QbD is a structured and systematic framework that is based on the principle that quality should be built into the product rather than be tested at a terminal stage in the product development. The ICH guidelines Q8 R(2), Q9, and Q10 delineate the strategy adopted by QbD, which leads to a thorough understanding of the product and process. The Quality Target Product Profile (QTTP), dissolution and maintenance of supersaturation, amorphous/crystalline ratio, bioavailability (pharmacokinetic characteristics), sterility, shelf-life, assay and content uniformity should be considered during application of QbD for development of cellulose based amorphous solid dispersions. Post finalization of QTTP, Critical Quality Attributes (CQAs) can be derived from the QTTP, prior knowledge, and initial risk assessment. CQAs affecting the performance of the amorphous solid dispersions are described in the fish-bone diagram (Fig. 5). Among these CQAs, those related to polymers are found to play a critical role in the development and performance of amorphous solid dispersions. Hence, selection of the polymer is one of the most crucial steps in the formulation of amorphous solid dispersions, as it significantly impacts the efficacy of the product. Although cellulose based polymers and their derivatives are considered as inert substances, newly developed cellulose derivatives may raise concern regarding the safety and toxicity based on the manner by which they interact with the drug or biological surroundings. Therefore, USFDA has published a list in the code of federal regulations (CFR) for GRAS substances that are generally regarded as safe. Over the years, the agency has also maintained a list entitled inactive ingredient database (IID) for excipients that have been approved and incorporated in the marketed products. Both GRAS and IID information can be useful to the industry as an aid in developing cellulose based amorphous solid dispersions. In general, non-clinical and clinical studies are required to demonstrate the safety of new excipients before use. In this context, USFDA has recently published guidance for industry on the conduct of non-clinical studies for the safety evaluation of new pharmaceutical excipients. This guidance highlights the importance of performing risk-benefit assessment on the newly proposed excipients in the drug products while establishing the permissible and safety limit for the excipients. Cellulose derivatives like HPMC, HPMCAS, HPMCP, CMC, and CMCAB are considered to be relatively safe and their acceptable limits are available in IID. However, for the newly synthesized cellulose derivatives, it is mandatory to report the toxicity profile of the polymer including the maximum permissible limits, before using them in the pharmaceutical products.
6. Conclusions

Use of cellulose derivatives as stabilizers in the development of amorphous solid dispersions of poorly soluble drugs has been a major area of interest for formulation scientists. The wide range of cellulosic polymers used as stabilizers in the marketed products validates their potential and assures that the cellulosic polymers and their derivatives are here to stay. Unique properties such as high molecular weight, hydrophilicity and hydrolytic stability make them ideal candidates for the development of polymeric dispersions. Significant efforts have been undertaken to understand the mechanism of crystallization inhibition in the solid and solution state at a molecular level. This review intends to guide the formulation scientist in appropriate selection of polymer for the development of amorphous solid dispersions by avoiding extensive screening experiments, thereby saving time.

Conflict of interest

Authors declare no conflict of interest.

Acknowledgments

The authors acknowledge the financial support from the Department of Pharmaceuticals (DoP), Ministry of Chemicals and Fertilizers, Govt. of India.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajps.2018.09.003.

REFERENCES

[1] Konno H, Taylor LS. Ability of different polymers to inhibit the crystallization of amorphous felodipine in the presence of moisture. Pharm Res 2008;25(4):969–78.
[2] Jermain SV, Brough C, Williams RO. Amorphous solid dispersions and nanocrystal technologies for poorly water-soluble drug delivery—an update. Int J Pharm 2018;535(1-2):379–92.
[3] Tanno F, Nishiyama Y, Kokubo H, Obara S. Evaluation of hypromellose acetate succinate (HPMCAS) as a carrier in solid dispersions. Drug Dev Ind Pharm 2004;30(1):9–17.
[4] Arca HC, Mosquera-Giraldo LI, Taylor LS, Edgar KJ. Synthesis and characterization of alkyl cellulose ω-carboxyesters for amorphous solid dispersion. Cellulose 2017;24(2):609–25.

[5] Alonzo DE, Raina S, Zhou D, Gao Y, Zhang GZ, Taylor LS. Characterizing the impact of hydroxypropylmethyl cellulose on the growth and nucleation kinetics of felodipine from supersaturated solutions. Cryst Growth Des 2012;12(3):1538–47.

[6] Arca HC, Mosquera-Giraldo LI, Pereira JM, Sriranganathan N, Taylor LS, Edgar KJ. Rifampin stability and solution concentration enhancement through amorphous solid dispersion in cellulose ω-carboxyalkanoate matrices. J Pharm Sci 2018;107(1):127–38.

[7] Xie T, Taylor LS. Improved release of celecoxib from high drug loading amorphous solid dispersions formulated with polyacrylic acid and cellulose derivatives. Mol Pharm 2016;13(3):873–84.

[8] Sharma P, Modi SR, Bansal AK. Co-processing as a tool to improve aqueous dispersibility of cellulose ethers. Drug Dev Ind Pharm 2015;41(11):1745–58.

[9] Edgar KJ, Buchanan CM, Debenham JS, et al. Advances in cellulose ester performance and application. Prog Polym Sci 2001;26(9):1605–88.

[10] Liu H, Taylor LS, Edgar KJ. The role of polymers in oral bioavailability enhancement; a review. Polym Adv Technol 2015;27(3):399–415.

[11] Curatolo WJ, Nightingale JAS, Shanker R.M., Sutton S.C. Basic drug compositions with enhanced bioavailability. 2003, Google Patents, US6548558B1.

[12] Kennedy M, Hu J, Gao P, et al. Enhanced bioavailability of a poorly soluble VR1 antagonist using an amorphous solid dispersion approach: a case study. Mol Pharm 2008;5(6):981–93.

[13] Yin L, Hillmyer MA. Preparation and performance of hydroxypropyl methylcellulose esters of substituted succinates for in vitro supersaturation of a crystalline hydrophobic drug. Mol Pharm 2013;11(1):175–85.

[14] Heinez T, Koschella A. Carboxymethyl ethers of cellulose and starch—a review. Macromol Symp 2005;223(1):13–40.

[15] Shelton MC, Posey-Dowty JD, Lingerfelt L, Kirk SK, Klein S, Edgar KJ. Enhanced dissolution of poorly soluble drugs from solid dispersions in cellulose carboxymethyl cellulose acetate butyrate matrices. Polysaccharide Mater: Perform Des 2009;1017:93–113.

[16] Malm CJ, Fordyce CR. Cellulose esters of dibasic organic acids. Ind Eng Chem 1940;32(3):405–8.

[17] DiNunzio JC, Miller DA, Yang W, McGinity JW, Williams RO 3rd. Amorphous compositions using concentration enhancing polymers for improved bioavailability of itraconazole. Mol Pharm 2008;5(6):968–80.

[18] Kar N, Liu H, Edgar KJ. Synthesis of cellulose adipate derivatives. Biomacromolecules 2011;12(4):1106–15.

[19] Liu H, Ilevbare GA, Cherniawski BP, Ritchie ET, Taylor LS, Edgar KJ. Synthesis and structure-property evaluation of cellulose ω-carboxyesters for amorphous solid dispersions. Carbohydr Polym 2014;100:116–25.

[20] Chiou WL, Riegelman S. Pharmaceutical applications of solid dispersion systems. J Pharm Sci 1971;60(9):1281–302.

[21] Qian F, Huang J, Hussain MA. Drug-polymer solubility and miscibility: stability consideration and practical challenges in amorphous solid dispersion development. J Pharm Sci 2010;99(7):2941–7.

[22] Rumphord AC, Ivanisevic I, Bates S, Alonzo DE, Taylor LS. Evaluation of drug-polymer miscibility in amorphous solid dispersion systems. Pharm Res 2009;26(11):2523–34.

[23] Gupta P, Kakumanu VK, Bansal AK. Stability and solubility of celecoxib-PVP amorphous dispersions: a molecular perspective. Pharm Res 2004;21(10):1762–9.

[24] Hancock BC, Zografi G. Characteristics and significance of the amorphous state in pharmaceutical systems. J Pharm Sci 1997;86(1):1–12.

[25] Kaushal AM, Gupta P, Bansal AK. Amorphous drug delivery systems: molecular aspects, design, and performance. Crit Rev Ther Drug Carr Syst 2004;21(3):133–93.

[26] Gao P, Akrami A, Alvarez F, et al. Characterization and optimization of AMG 517 supersaturatable self-emulsifying drug delivery system (S-SEDDS) for improved oral absorption. J Pharm Sci 2009;98(2):516–28.

[27] Ilevbare GA, Liu H, Edgar KJ, Taylor LS. Inhibition of solution crystal growth of ritonavir by cellulose polymers-factors influencing polymer effectiveness. CrystEngComm 2012;20(4):563–14.

[28] Ilevbare GA, Liu H, Edgar KJ, Taylor LS. Maintaining supersaturation in aqueous drug solutions: impact of different polymers on induction times. Cryst Growth Des 2012;13(2):740–51.

[29] Chauhan H, Hui-Gu C, Atef E. Correlating the behavior of polymers in solution as precipitation inhibitor to its amorphous stabilization ability in solid dispersions. J Pharm Sci 2013;102(6):1924–35.

[30] Oucherif KA, Raina S, Taylor LS, Listter JD. Quantitative analysis of the inhibitory effect of HPMC on felodipine crystalization kinetics using population balance modeling. CrystEngComm 2013;15(12):2197–205.

[31] Chavan RB, Thipparaboina R, Kumar D, Shastri NR. Evaluation of the inhibitory potential of HPMC, PVP and HPC polymers on nucleation and crystal growth. RSC Adv 2016;6(81):77569–76.

[32] Friesen DT, Shanker R, Crew M, Smithey DT, Curatolo WJ, Nightingale JA. Hydroxypropyl methylcellulose acetate succinate-based spray-dried dispersions: an overview. Mol Pharm 2008;5(6):1003–19.

[33] Riedel A, Leopold C. Degradation of omeprazole induced by enteric polymer solutions and aqueous dispersions: HPLC investigations. Drug Dev Ind Pharm 2005;31(2):151–160.

[34] Schram CJ, Taylor LS, Beaudoin SP. Influence of polymers on the crystal growth rate of felodipine: correlating adsorbed indomethacin surface coverage to solution crystal growth inhibition. Langmuir 2015;31(41):11279–87.

[35] Schram CJ, Smyth RJ, Taylor LS, Beaudoin SP. Understanding crystal growth kinetics in the absence and presence of a polymer using a rotating disk apparatus. Cryst Growth Des 2016;16(5):2640–5.

[36] Schram CJ, Beaudoin SP, Taylor LS. Polymer inhibition of crystal growth by surface poisoning. Cryst Growth Des 2016;16(4):2094–103.

[37] Schram CJ, Beaudoin SP, Taylor LS. Impact of polymer conformation on the crystal growth inhibition of a poorly water-soluble drug in aqueous solution. Langmuir 2014;31(1):171–9.

[38] Xie T, Taylor LS. Dissolution performance of high drug loading celecoxib amorphous solid dispersions formulated with polymer combinations. Pharm Res 2016;33(3):739–750.

[39] Ueda K, Higashi K, Yamamoto K, Moribe K. Inhibitory effect of hydroxypropyl methylcellulose acetate succinate on drug recrystallization from a supersaturated solution assessed using nuclear magnetic resonance measurements. Mol Pharm 2013;10(10):3801–11.

[40] Ricarte RG, Li Z, Johnson LM, et al. Direct observation of nanostructures during aqueous dissolution of polymer/drug particles. Macromolecules 2017;50(8):3143–52.

[41] Huang W, Mandal T, Larson RG. Multiscalar computational modeling of the nanostructure of solid dispersions of...
hydroxypropyl methylcellulose acetate succinate (HPMCAS) and phenyltoin. Mol Pharm 2017;14(10):3422–35.

[42] Ilevbare GA, Liu H, Edgar KJ, Taylor LS. Impact of polymers on crystal growth rate of structurally diverse compounds from aqueous solution. Mol Pharm 2013;10(6):2381–93.

[43] Li B, Konecke S, Wegiel LA, Taylor LS, Edgar KJ. Both solubility and chemical stability of curcumin are enhanced by solid dispersion in cellulose derivative matrices. Carbohydr Polym 2013;98(1):1108–16.

[44] Ren F, Sun H, Cui L, et al. Antisolvent recrystallization strategy to screen appropriate carriers to stabilize filgotinib amorphous solid dispersions. J Pharm Sci 2018;107(6):1624–32.

[45] Vasconcelos T, Marques S, Neves J, Sarmento B. Amorphous solid dispersions: rational selection of a manufacturing process. Adv Drug Deliv Rev 2016;100:85–101.

[46] Chavan RB, Thipparaboina R, Kumar D, Shastri NR. Co amorphous systems: a product development perspective. Int J Pharm 2016;515(1-2):403–15.

[47] Serajuddin AT. Solid dispersion of poorly water-soluble drugs: early promises, subsequent problems, and recent breakthroughs. J Pharm Sci 1999;88(10):1058–66.

[48] Rumondor AC, Stanford LA, Taylor LS. Effects of polymer type and storage relative humidity on the kinetics of felodipine crystallization from amorphous solid dispersions. Pharm Res 2009;26(12):2599.

[49] Nie H, Su Y, Zhang M, et al. Solid-state spectroscopic investigation of molecular interactions between Clofazimine and Hypromellose phthalate in amorphous solid dispersions. Mol Pharm 2016;13(11):3964–75.

[50] Konno H, Taylor LS. Influence of different polymers on the crystallization tendency of molecularly dispersed amorphous felodipine. J Pharm Sci 2006;95(12):2692–2705.

[51] Patel DD, Joguparthi V, Wang Z, Anderson BD. Maintenance of supersaturation I: Indomethacin crystal growth kinetic modeling using an online second-derivative ultraviolet spectroscopic method. J Pharm Sci 2011;100(7):2623–41.

[52] Li B, Liu H, Amin M, Wegiel LA, Taylor LS, Edgar KJ. Enhancement of naringenin solution concentration by solid dispersion in cellulose derivative matrices. Cellulose 2013;20(4):2137–49.

[53] Ozaki S, Kushida I, Yamashita T, Hasebe T, Shirai O, Kano K. Inhibition of crystal nucleation and growth by water-soluble polymers and its impact on the supersaturation profiles of amorphous drugs. J Pharm Sci 2013;102(7):2273–81.

[54] Li B, Konecke S, Harich K, Wegiel L, Taylor LS, Edgar KJ. Solid dispersion of quercetin in cellulose derivative matrices influences both solubility and stability. Carbohydr Polym 2013;92(2):2033–40.

[55] Patel DD, Anderson BD. Maintenance of supersaturation II: Indomethacin crystal growth kinetics versus degree of supersaturation. J Pharm Sci 2013;102(5):1544–53.

[56] Trasi NS, Oucherif KA, Litster JD, Taylor LS. Evaluating the influence of polymers on nucleation and growth in supersaturated solutions of acetaminophen. CrystEngComm 2015;17(6):1242–9.

[57] Dong Y, Mosquera-Giraldo LI, Taylor LS, Edgar KJ. Amphipilic cellulose ethers designed for amorphous solid dispersion via olefin cross-metathesis. Biomacromolecules 2016;17(2):454–65.

[58] Jackson MJ, Kestur US, Hussain MA, Taylor LS. Characterization of supersaturated danazol solutions—impact of polymers on solution properties and phase transitions. Pharm Res 2016;33(5):1276–88.

[59] Dong Y, Mosquera-Giraldo LI, Troutman J, Skogstad B, Taylor LS, Edgar KJ. Amphipilic hydroxylalkyl cellulose derivatives for amorphous solid dispersion prepared by olefin cross-metathesis. Polym Chem 2016;7(30):4953–63.

[60] Gilley AD, Arca HC, Nichols BLB, et al. Novel cellulose-based amorphous solid dispersions enhance quercetin solution concentrations in vitro. Carbohydr Polym 2017;157:86–93.

[61] Xie T, Gao W, Taylor LS. Impact of Eudragit EPO and hydroxypropyl methylcellulose on drug release rate, supersaturation, precipitation outcome and redissolution rate of indomethacin amorphous solid dispersions. Int J Pharm 2017;531(1):313–23.

[62] Winslow CJ, Nichols BLB, Novo DC, et al. Cellulose-based amorphous solid dispersions enhance rifampicin delivery characteristics in vitro. Carbohydr Polym 2017;185:149–158.

[63] Hong S, Nowak SA, Wah CL. Impact of physicochemical properties of cellulotic polymers on supersaturation maintenance in aqueous drug solutions. AAPS PharmSciTech 2018;19(4):1860–8.

[64] Konno H, Handa T, Alonzo DE, Taylor LS. Effect of polymer type on the dissolution profile of amorphous solid dispersions containing felodipine. Eur J Pharm Biopharm 2008;70(2):493–9.

[65] Alonzo DE, Zhang GG, Zhou D, Gao Y, Taylor LS. Understanding the behavior of amorphous pharmaceutical systems during dissolution. Pharm Res 2010;27(4):608–18.

[66] Erdenbrugh V, Taylor LS. An ab initio polymer selection methodology to prevent crystallization in amorphous solid dispersions by application of crystal engineering principles. CrystEngComm 2011;13(20):6171–8.

[67] Trasi NS, Taylor LS. Effect of polymers on nucleation and crystal growth of amorphous acetaminophen. CrystEngComm 2012;14(16):5188–97.

[68] Raina SA, Alonzo DE, Zhang GG, Gao Y, Taylor LS. Impact of polymers on the crystallization and phase transition kinetics of amorphous nimodipine during dissolution in aqueous media. Mol Pharm 2014;11(10):3565–76.

[69] Hsieh YL, Box K, Taylor LS. Assessing the impact of polymers on the pH-induced precipitation behavior of poorly water soluble compounds using synchrotron wide angle X-ray scattering. J Pharm Sci 2014;103(9):2724–35.

[70] Chen Y, Liu C, Chen Z, et al. Drug–polymer–water interaction and its implication for the dissolution performance of amorphous solid dispersions. Mol Pharm 2015;12(2):576–589.

[71] Sarode AL, Malekar SA, Cote C, Worthen DR. Hydroxypropyl cellulose stabilizes amorphous solid dispersions of the poorly water soluble drug felodipine. Carbohydr Polym 2014;112:512–19.

[72] Raina SA, Van Erdenbrugh B, Alonzo DE, et al. Trends in the precipitation and crystallization behavior of supersaturated aqueous solutions of poorly water-soluble drugs assessed using synchrotron radiation. J Pharm Sci 2015;104(6):1981–1992.

[73] Sato T, Taylor LS. Chiral discrimination by a cellulose polymer: differential crystallization inhibition of enantiomers in amorphous dispersions. CrystEngComm 2015;17(27):5046–53.

[74] Wegiel LA, Mosquera-Giraldo LI, Mauer LJ, Edgar KJ, Taylor LS. Phase behavior of resveratrol solid dispersions upon addition to aqueous media. Pharm Res 2015;32(10):3324–37.

[75] Zhang S, Britten JS, Chow AHIL, Lee TWY. Impact of crystal structure and polymer excipients on the melt crystallization kinetics of itraconazole polymorphs. Cryst Growth Des 2017;17(6):3433–42.
[76] Ueda K, Higashi K, Moribe K. Direct NMR monitoring of phase separation behavior of highly supersaturated nifedipine solution stabilized with hypromellose derivatives. Mol Pharm 2017;14(7):2314–22.

[77] Chavan RB, Lodagekar A, Shastri NR. Determination of precipitation inhibitory potential of polymers from amorphous solid dispersions. Drug Dev Ind Pharm 2018. doi:10.1080/03639045.2018.1503295.

[78] Lehmkemper K, Kyeremateng SO, Bartels M, Degenhardt M, Sadowski G. Physical stability of api/polymer-blend amorphous solid dispersions. Eur J Pharm Biopharm 2018;124:147–57.

[79] Fan N, He Z, Ma P, et al. Impact of HPMC on inhibiting crystallization and improving permeability of curcumin amorphous solid dispersions. Carbohydr Polym 2018;181:543–50.