Chapter 8

Cellulose and Its Derivatives Use in the Pharmaceutical Compounding Practice

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Additional information is available at the end of the chapter

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1. Introduction

For centuries, the pharmaceutical profession has provided services of fundamental value to society, such as the procurement, storage, compounding and dispensing of drugs. In recent decades, the focus of the pharmacist's role has shifted from compounding medicines to ensuring their safe and effective use by providing information and advice [1,2]. Although compounding activity has decreased over time, it is incontestable that this service is essential in certain patient specific situations, where industrially produced medicine is not available or is inappropriate for a particular reason [3,4]. Thus, compounded medicines are mainly important for paediatric and geriatric patients, and patients with special needs such as those with dermatological diseases [3,5,6,7,8]. In many countries, nowadays, the activity of compounding is a complementary practice to the production of medicines in alternative amounts and diversified dosage forms (liquid, semi-solid, solid) in community pharmacies (United States of America, The Netherlands), as well as in hospital pharmacies (Canada, France, Belgium, Croatia, Denmark, England, Finland, Germany, Ireland, Italy, Norway, Scotland, Slovenia, Spain, Sweden, Switzerland) [3,4,8-10].

Interestingly, compounded medicines were estimated to make up 10-15% of all dispensed drugs in the Netherlands in the early 90's, 5.5% in 1994 and 6.6% in 1995. By the year 2000 this estimate was 3.7-5.5% [3]. On the other hand, the compounding field appears to have been a considerable and growing business since the 1990's in the United States. These products represented around 1% of all prescriptions dispensed yearly and according to this estimate, 30 million medications would have been compounded in 2003 [4]. This shows that the population has recognized that compounding pharmacies can provide individualized drug therapy benefits [11].

The practice of compounding requires not only the drug(s) (active pharmaceutical ingredient, API), but also, the excipient(s) (pharmacological inert component) in order to

obtain the final medicine. The excipients are chosen according to the characteristics of the required dosage form [5]. Each excipient exerts specific functions in the formulation, as, for instance, a diluent for hard capsules or powders, a coating agent for solid oral dosage forms, a suspending, thickening or stabilizing agent for oral liquids, etc. The excipient function depends on the concentration in a particular pharmaceutical formulation [12,13].

Cellulose (Figure 1) and its derivatives (ether and ester) are among the excipients frequently used in pharmaceutical compounded and industrialized products with various purposes. Among their uses, the most frequently reported are as suspending agents in oral liquid extemporaneous preparation and as viscosity increasing agents in topical formulations, exemplified in Tables 1, 2 [5,7,8,14]. Particularly, in oral solid dosage forms, cellulose and its derivatives (also known as cellulosics) can render distinct drug delivery property patterns: immediate, controlled/sustained or delayed release [15,16]. In addition, cellulosics show several interesting characteristics such as low cost, reproducibility, biocompatibility, and recyclability [16]. The latter is currently an important aspect considering the need for green technology.

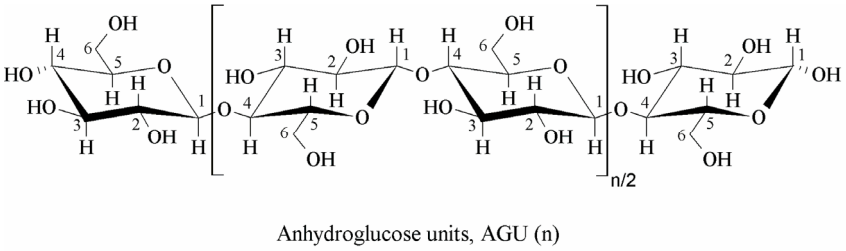
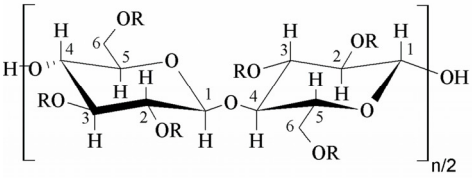


Figure 1. The chemical structure of cellulose with two β-1,4 linked anhydroglucose units.

Cellulose is the most abundant biopolymer. It is present in the cell walls of a great diversity of organisms, from bacteria (Cyanobacteria), prokaryotes (*Acetobacter, Rhizobium, Agrobacterium*) to eukaryotes (fungis, amoebae, green algae, freshwater and marine algae, mosses, ferns, angiosperms, gymnosperms). It is also produced by some animals, the tunicates (urochordates), members of the subphylum Tunicata in the Chordata phylum [17-19]. Native cellulose made by biosynthesis in living organisms is composed only of glucose monomers, as anhydroglucose (AGU) or glucan units ($C_6H_{10}O_5$, n) with β-1,4 linkages (Figure 1). It usually exists as cellulose I (in most plants) and rarely as cellulose II (in several algae and some bacteria) allomorphs, in which the glucan chains are oriented parallel and antiparallel respectively [20, 21]. Cellulose allomorphs (I, II, III_I, III_{II}, IV_I, IV_{II}) have structural variations regarding unit cell dimensions, degree of intra/interchain hydrogen bonding per unit cell and polarity of adjacent cellulose sheets [22]. Cellulose I allomorphs consist of distinct numbers of parallel glucan chains arranged to form nanofibrils. Native crystalline cellulose I has two suballomorphs, α and β, which exist as a single chain triclinic unit cell and a two chain monoclinic unit cell, respectively. Cellulose I β is rarely synthesized in nature as a pure form (except by tunicates) and is more thermodynamically stable [20]. Cellulose I can be altered by a strong alkali treatment in order to produce other crystalline

forms, II, III and IV. Cellulose II is the allomorph that is thermodynamically most stable [16,23-24]. Cellulose III can be prepared by liquid ammonia or (mono, di, tri) amine treatment of cellulose I and II [25]. The cellulose IV crystalline form is obtained by immersion in glycerol and heating of cellulose III [26]. Cellulose is an excipient widely employed by both pharmaceutical companies (tablet processing) and compounding pharmacies; it is available in powdered (n≈500) and microcrystalline (n≈220) forms, the latter being obtained by acid hydrolysis of the amorphous regions of the cellulose nanofibrils.

Cellulosics, such as methyl, ethyl, hydroxyethyl, hydroxyethylmethyl, hydroxypropyl (HP), hydroxypropyl methyl (HPM, also denominated hypromellose) and carboxymethyl ethers cellulose (Figure 2) are formed by hydroxyl etherification with the appropriate alkyl halide (R-Cl, see Figures 2, 3) from previously alkalinized cellulose usually obtained from wood pulp [16]. The degree of substitution (DS) in these ether derivatives indicates the average number of R groups present in each glucan unit along the chain. The maximum DS is three, since it is the number of hydroxyl groups that can be substituted on each glucan unit. DS affects cellulose derivatives' physical properties such as solubility [12].



Cellulose ethers	R groups
Methylcellulose	H, CH_3
Ethylcellulose	H, CH_2CH_3
Hydroxyethylmethylcellulose	H, CH_3, $[CH_2CH_2O]_nH$
Hydroxypropylcellulose	H, $[CH_2CH(CH_3)O]_nH$
Carboxymethylcellulose	H, CH_2COONa

Figure 2. Chemical structure of cellulose ether derivatives.

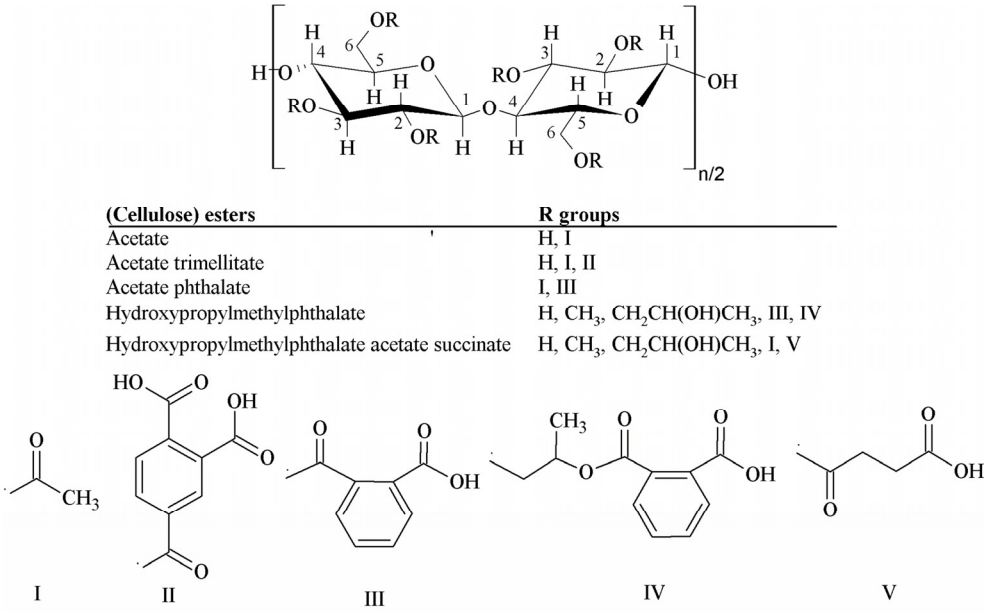
Cellulose derivatives are employed as excipients in pharmaceutical industrial products for oral, topical or parenteral administration [12,16,27]. Their most relevant application, as observed in pharmaceutical industrial products, is to create matrix systems for solid oral dosage forms. Due to their aqueous swelling, the drug release is controlled by its diffusion through the hydrogel layers that are formed. For instance, the use of carboxymethyl cellulose (CMC) sodium salt as an excipient sustains the release in solid oral dosage forms.

Cellulosics, such as the cellulose esters acetate, acetate trimellitate, acetate phthalate (CAP), HPM phthalate, HPM acetate succinate are formed by hydroxyl esterification with either acetic, trimellitic, dicarboxylic phthalic or succinic acids, or a combination of them, as represented in Figure 3. The reaction usually occurs in the presence of a strong acid that promotes the acid catalysis.

Among these cellulosics, CAP was one of the earliest and most effective solutions to pH-controlled release, and its use still continues today [15]. These cellulosics are usually resistant to acid environments such as that of the stomach and are thus very useful as enteric coatings for capsules or tablets [12,16]. Cellulose esters require plasticizers (acetylated monoglyceride, butyl phtalylbutyl glycolate, dibutyl tartrate, diethyl phthalate, dimethyl phthalate, ethyl phthalylethyl glycolate, glycerin, propylene glycol, triacetin, triacetin

citrate, triethylcitrate, tripropionin) soluble in organic solvents (ketones, esters, ether alcohols, cyclic ethers) or in their mixtures, such as methanol/chloroform and ethyl acetate/isopropanol in order to produce more effective coating films [12,28,29]. Some of the cellulose esters are employed either in industrial or compounded pharmaceutical preparations.

Some cellulosics, if they are to be applied in distinct drug delivery formulations, may require special large scale processing and equipment normally only installed in pharmaceutical industry plants. This is one of the reasons why not all commercially available cellulosics are employed in compounding pharmacies. A description of some cellulosics and their applications in compounded medicines is presented in the following sections.



(Cellulose) esters	R groups
Acetate	H, I
Acetate trimellitate	H, I, II
Acetate phthalate	I, III
Hydroxypropylmethylphthalate	H, CH_3, $CH_2CH(OH)CH_3$, III, IV
Hydroxypropylmethylphthalate acetate succinate	H, CH_3, $CH_2CH(OH)CH_3$, I, V

Figure 3. Chemical structures of cellulose ester derivatives.

2. Cellulose and its derivatives in compounded medicines

2.1. Cellulose

Powdered cellulose and microcrystalline cellulose come from α-cellulose (cellulose free of hemi-celluloses and lignin) pulp from fibrous plant materials; they differ in regard to their manufacturing processes. Powdered cellulose is obtained by α-cellulose purification and mechanical size reduction. Crystalline cellulose is obtained by controlled hydrolysis of α-cellulose with mineral acid solutions (2 to 2.5 N), followed by hydrocellulose purification by filtration and spray-drying of the aqueous portion [12].

In compounded medicines, powdered cellulose and microcrystalline cellulose are used as an adsorbent, a suspending agent, a capsule diluent (5-30% and 20-90%, respectively). Powdered cellulose is also used as a thickening agent.

The applications of the powdered cellulose and the microcrystalline cellulose in compounding pharmacies include the oral solid dosage form (capsules) as a bulking agent to increase the mass in formulations containing small amounts of the active ingredient. The powdered cellulose is a base material for powder dosage forms, a suspending agent for aqueous peroral delivery and an adsorbent and thickening agent for topic preparations [12]. Moreover, the microcrystalline cellulose is a constituent of the vehicle used for oral suspension [27].

2.2. Cellulose ether derivatives

2.2.1. Methylcellulose (MC)

In this cellulose ether derivative approximately 27–32% of hydroxyl groups are changed to the methyl ether (CH_3O) form. MC is practically insoluble in most organic solvents. Various grades of MC can be found with degrees of polymerization in the range of 50 to 1000 and molecular weights (number average) in the range 10 000 to 220 000 Da [12].

In compounded medicines, MCs function as emulsifying agents (1-5%), suspending agents (1-2%), capsule disintegrants and viscosity increasing agents.

In compounding pharmacies, MCs of different viscosity grades, low and high, have been applied in oral liquid (oil emulsions, suspensions, solutions) and topical (creams, gels) formulations respectively. MC is often used instead of sugar-based syrups and other suspension bases. MC delays the settling of suspensions and increases the contact time of drugs in the stomach [12].

2.2.2. Ethylcellulose (EC)

This cellulose derivative is partially or completely ethoxylated, yielding 44-51% of ethoxyl groups (OCH_2CH_3). Full substitution (DS=3) of cellulose units produce $C_{12}H_{23}O_6(C_{12}H_{22}O_5)_nC_{12}H_{23}O_5$, where n can vary, thus providing a wide variety of molecular weights. EC is a long-chain polymer of ethyl-substituted β-glucan units joined together by glycoside linkages [12].

In compounded medicines, EC functions as a flavouring and as a viscosity increasing agent.

In compounding pharmacies, EC finds applications in oral and topical (creams, lotions, gels) formulations. For oral use, it works as an active delivering agent and for topical dosage forms as a thickening agent. It has been evaluated as a stabilizer for emulsions [12].

2.2.3. Hydroxyethylcellulose (HEC)

This cellulose derivative is a partially substituted hydroxyethyl (CH_2CH_2OH) ether of cellulose. It is found in various viscosity grades, with respect to the DS and molecular

weight. Some grades are modified so as to improve aqueous dispersion. HEC is insoluble in most organic solvents.

In compounded medicines, HEC has the following functions: a suspending, a thickening and a viscosity-increasing agent.

It is widely employed in topical formulations (gel) and cosmetics due to its nonionic and water-soluble polymer characteristics. The main use is as a thickening agent [12].

2.2.4. Hydroxypropylcellulose (HPC)

This cellulose derivative is partially hydroxypropylated, yielding 53.4–80.5% of hydroxypropyl groups [$OCH_2CH(OH)CH_3$]. Because the added hydroxypropyl contains a hydroxyl group which can also be etherified during the preparation, the degree of substitution of hydroxypropyl groups can be higher than three. HPC is found in different grades that provide solutions with various viscosities. Its molecular weight has a range of 50 000 to 1 250 000. HPC with an value of moles of substitution of approximately four is necessary in order to have good water solubility.

In compounded medicines, HPC is used as an emulsifying, a stabilizing, a suspending, a thickening or a viscosity-increasing agent.

In compounding pharmacies, HPC is also employed in topical formulations (gel) and especially in cosmetics, as an emulsifier and a stabilizer [12].

2.2.5. Hydroxypropylmethylcellulose (HPMC)

This cellulose derivative, also called hypromellose, is a partly O-methylated and O-(2-hydroxypropylated) cellulose. HPMC is found in various grades with different viscosities and extents of substitution. The content of methoxyl (OCH_3) and hydroxypropyl groups [$OCH_2CH(OH)CH_3$] affects the HPMC molecular weight, which ranges from 10 000 to 1 500 000.

HPMC has many different functions in compounded medicines as a dispersing, an emulsifying, a foaming, a solubilizing, a stabilizing, a suspending (0.25-5%) and a thickening (0.25-5%) agent. In addition, HPMC can be applied as a controlled-release and sustained-release agent.

In compounding pharmacies, HPMC has found application for nasal (liquid) and topical (gel, ointment) formulations as a thickening, a suspending, an emulsifying and a stabilizing agent. The aqueous solution produced with HPMC presents greater clarity and fewer undissolved fibres compared with MC. HPMC can prevent droplets and particles from coalescing or agglomerating, thus inhibiting the formation of sediment. In addition, it is also widely used in cosmetics [12].

2.2.6. Carboxymethyl cellulose (CMC)

It is available as calcium and sodium salt forms of a polycarboxymethyl (CH_2COOX, X=Ca or Na) ether of cellulose. Only sodium CMC is commonly used in compounded preparations. The degree of substitution can be estimated by a sodium assay, which must be between 6.5-9.5%.

CMC-Na acts as a capsule disintegrant and a stabilizing, a suspending, an emulsifying (0.25-1%), a gel-forming (3-6%) and a viscosity-increasing (0.1-1%) agent in compounded medicines.

In compounding pharmacies, CMC-Na has applications in oral (liquid, solid) and topical (liquid, gel, emulsion) formulations, primarily for its viscosity-increasing properties. Viscous aqueous solutions are used to suspend powders intended for either topical or oral use. In emulsions, CMC may be used as stabilizer. At higher concentrations, a CMC of intermediate-viscosity grade forms gels that are employed as a base for cosmetics or other drug formulations [12]. Similarly to microcrystalline cellulose, CMC-Na is also described as a constituent of vehicles used for oral suspension [27].

2.3. Cellulose ester derivatives

2.3.1. Cellulose acetate

This cellulose derivative has partially or completely acetylated ($COCH_3$) hydroxyl groups. Cellulose acetate is available in a wide range of acetyl levels (29-44.8%) and chain lengths, with molecular weights ranging from 30 000 to 60 000.

Cellulose acetate is used as a capsule diluent, a filler and as a taste-masking agent in compounded medicines [12].

2.3.2. Cellulose acetate phthalate (CAP)

CAP acid form is a cellulose derivative obtained by the reaction of phthalic anhydride and a partial acetate ester of cellulose. It contains 21.5–26% of acetyl ($COCH_3$) and 30-36% of phthalyl (o-carboxybenzoyl, COC_6H_4COOH) groups.

In compounded medicines, CAP confers gastro-resistance, and is thus used as an enteric coating agent (0.5-9%) [12].

In compounding pharmacies, CAP has applications in oral solid dosage forms either by film coating from organic (ketones, esters, ether alcohols, cyclic ethers) or aqueous solvent systems. Such coatings resist prolonged contact with the strongly acidic gastric fluid, but dissolve in the mildly acidic or neutral intestinal environment. The addition of plasticizers improves the water resistance of such coating materials, making formulations with this derivative more effective [12,29].

As mentioned, cellulose and its derivatives, primarily intended for use in the pharmaceutical industry, are also relevant in compounding practice. The common uses of cellulosics in compounding practices as a diluent in solid dosage forms, a thickening and a

suspending agent in liquid dosage forms, an emulsifying agent in semi-solid preparations and others require well known manufacturing techniques, which do not need sophisticated apparatus [5]. Nevertheless, specific equipment may be necessary when cellulosics are employed to impart special dosage form properties, such as in modified release systems. Among the modified drug delivery systems, mostly delayed and controlled (extended or slow) release have been described in compounding practice. In the former, the systems are frequently employed to prevent drug degradation in acid environments after oral administration, to protect the stomach mucosa from drug irritation and to release the drug in the intestine. In controlled release, systems are used to prevent side effects and to reduce the number of daily administrations [29,30].

CAP is the cellulosic most frequently mentioned in compounded delayed-release dosage forms [31-33]. The use of sodium carboxymethylcellulose or hydroxypropyl methylcellulose have also been reported in extended or slow-release systems [34-40]. These systems are most commonly obtained by the simple mixing of the drug with an appropriate inert matrix [39]. The Food and Drug Administration (FDA) warns that in some instances, compounders may lack sufficient control techniques and resources (equipment, training, testing or facilities) to assure product quality or to compound more elaborated products such as modified release drugs [4]. Since obtaining high quality, safe and effective products is fundamental, compounding techniques must be developed and standardized. Thus, coating techniques used to obtain delayed release compounded capsules by the beaker flask method, by dipping or by spraying have been proposed [41]. In beaker flask coating, a small amount of coating material is added to the beaker and heated until melted. Subsequently, a few capsules are added away from the heat and the beaker is manually rotated to coat them. Small quantities of coating material are continuously added in order to prevent the capsules from sticking. The immersion or dipping method consists of heating the coating material in a recipient that permits the dipping of the capsules with the aid of tweezers in the coating solution and subsequent hardening. This process is repeated until all the capsules have a homogenous film. The vaporization or atomization method, also called spraying, consists in preparing a solution of the coating material in alcohol, ether, or keto-alcoholic solvents and transferring it to a spray bottle. The capsules are held over a screen, under ventilation. The coating solution is applied in multiple thin layers that are allowed to dry between applications. A small scale piece of machinery exists for this coating process [33].

3. Review of the use of cellulosics in compounding

The use of cellulose and/or its derivatives as part of compounded formulations has been cited in a great number of studies in the literature. A review of their properties and usage in pharmaceutical preparations is presented in the following section. Focus is given to the products that require more elaborate techniques in compounding pharmacies.

3.1. Cellulose derivatives in oral liquid (suspensions) extemporaneous preparation

It is well known that children and the elderly have difficulties in swallowing solid dosage forms, due to their size or texture. Such population groups benefit from oral liquid

administration; hence, this is a preferred means of administration. Frequently, drugs in a concentration appropriate for paediatric use are unavailable or extemporaneous preparations from commercial products become a necessity. Thus, patients with special needs can be provided with drugs easily administered in the hospitals if extemporaneous preparations are compounded from drugs that are industrially produced.

Methylcellulose (1%) and simple syrup NF (as described in the United States Pharmacopeia National Formulary monograph) mixtures have been used as a vehicle for many extemporaneous oral drug suspensions prepared from commercial products (tablets or capsules) [27,41]. Compounded oral preparations can be obtained by finely grinding tablets or the content of capsules in a mortar and pestle, with the gradual addition of small volumes of the vehicle being mixed. The final volume can be adjusted in a graduated glass cylinder. Afterwards, the suspension is transferred to an appropriate plastic or glass bottle protected (amber) or not (transparent) from light.

Stability studies conducted at 4 °C and 25 °C for distinct drugs over at least 8 weeks are shown in Table 1 [42-52].

In such listed studies, suspensions containing MC did not show substantial changes in pH, odour or physical appearance in the period during which the drug content was assayed and found not to be less than 90% of the original concentration. This is a demonstration that MC formulations provide satisfactorily safe and stable products.

Oral extemporaneous suspensions of other drugs (amiodarone, granisetron, trimethoprim, and verapamil salt) prepared in methylcellulose and simple syrup (MC:SS) were also reported to have adequate stability [14].

Drug [Ref.]	Drug dosage form (mg)	Suspension (mg/mL)	MC:SS ratio	Stability (days) in different temperatures	
				4 °C	25 °C
Clonazepam [42]	Tablets (0.5, 1, 2)	0.1	NI	60[c]	NE
Gabapentin [43]	Capsules (100, 300, 400)	100	1:1	91[c]	56[c]
Nifedipine [44]	Capsules (10, 20)	4	1:13	91[b]	91[b]
Procainamide hydrochloride [45]	Capsules, tablets (250, 375, 500)	5, 50	70:30 Cherry syrup	180[b]	180[b]
Propylthiouracil [46]	Tablets (50)	5	1:1	91[c]	70[c]
Pyrazinamide [47]	Tablets (500)	100	1:1	60[b]	60[b]
Pyrimethamine [48]	Tablets (25)	2	1:1	91[a,c]	91[a,c]
Sildenafil citrate [49]	Tablets (25, 50, 100)	2.5	1:1	91[c]	91[c]
Sotalol hydrochloride [50,51]	Tablets (80, 120, 160, 240)	5	1:9	91[b]	91[b]
			2.4:1	84[a]	84[a]
Tiagabine hydrochloride [52]	Tablets (2, 4, 6, 8, 10, 12, 16)	1	1:6	91[c]	42[c]

a: amber glass, b: plastic; c: amber plastic bottles; NI, not informed; NE, not evaluated.

Table 1. Stability of different drugs in oral suspension extemporaneously prepared in a mixture of 1% methylcellulose:simple syrup (MC:SS) from commercial available products.

Another cellulose derivative frequently used as part of a vehicle in oral extemporaneous suspensions is sodium carboxymethylcellulose. It is a constituent of a commercial product, Ora-Plus®, which is employed in a 1:1 mixture with Ora-Sweet® (with sugar) or Ora-Sweet SF® (sugar free) [7,8]. Ora-Sweet® is a sugar-based citrus-berry flavoured syrup (see Table 2 footnote). Researchers have performed stability studies for various oral suspensions of drugs with this vehicle. The results of drug stability tests for periods of at least 8 weeks at refrigerated (3-5°C) and room (22-25°C) temperatures, are presented in Table 2 [43,46,49-77].

Drug [Ref.]	**Dosage form (mg)**	**Suspension (mg/mL)**	**CMC or Ora-Plus added (1:1) of**	**Stability (days) in different temperatures**	
				3-5°C	**22-25°C**
Acetazolamide [53,54]	Tablets (125, 250)	25[a]	Ora-Sweet® Ora-Sweet SF®	60[g]	60[g]
Allopurinol [54]	Tablets (100, 300)	20[a]			
Alprazolam [55]	Tablets (0.25, 0.5, 1, 2)	1[a]	Ora-Sweet® Ora-Sweet SF®	60[h]	60[h]
Azathioprine [54]	Tablets (50)	50[a]		60[g]	60[g]
Baclofen [56]	Tablets (10, 20)	10[a]		60[h]	60[h]
Bethanechol chloride [57]	Tablets (5, 10, 25, 50)	5[a]			
Captopril [56]	Tablets (12.5, 25, 50, 100)	0.75[a]		<10[h]	<10[h]
Chloroquine phosphate [55]	Tablets (250, 500)	15[a]		60[h]	60[h]
Cisapride [55]	Tablets (10, 20)	1[a]			
Clonazepam [54]	Tablets (0.5, 1, 2)	0.1[a]		60[g]	60[g]
Dapsone [58]	Tablets (25, 100)	2	Ora-Sweet®	91[e]	91[e]
Diltiazem HCl [56]	Tablets (30, 60, 90, 120)	12[a]	Ora-Sweet® Ora-Sweet SF®	60[h]	60[h]
Dipyridamole [56]	Tablets (25, 50, 75)	10[a]			
Dolasetron mesylate [59]	Tablets (50, 100)	10	Strawberry syrup Ora-Sweet SF®	90[e]	90[e]
Enalapril maleate [55]	Tablets (2.5, 5, 10, 20)	1[a]	Ora-Sweet® Ora-Sweet SF®	60[h]	60[h]
Famotidine [60]	Tablets (10, 20, 40)	8	Ora-Sweet®	NE	95[h]
Flecainide acetate [56]	Tablets (50, 100, 150)	20[a]	Ora-Sweet® Ora-Sweet SF®	60[h]	60[h]
Flucytosine [54]	Tablets (250, 500)	10[a]		60[g]	60[g]
Gabapentin [43]	Capsules (100, 300, 400)	100	Ora-Sweet®	91[e]	56[e]

Drug [Ref.]	Dosage form (mg)	Suspension (mg/mL)	CMC or Ora-Plus added (1:1) of	Stability (days) in different temperatures	
				3-5°C	22-25°C
Hydralazine HCl [55]	Tablets (10, 25, 50, 100)	4[a]	Ora-Sweet® Ora-Sweet SF®	1[h] 2[h]	unstable[h]
Ketoconazole [61]	Tablets (200)	20[a]		60[h]	60[h]
Labetalol HCl [62]	Tablets (100, 200, 300)	40[a]			
Lamotrigine [63]	Tablets (25, 100, 150, 200)	1		91[h]	91[h]
Levodopa + carbidopa [64]	Tablets (100+25)	5 2.5	Ora-Sweet®	42[e]	28[e]
Levofloxacin [65]	Tablets (200, 500, 750)	50	Strawberry syrup	57[e]	57[e]
Metolazone [61]	Tablets (2.5, 5, 10)	1[a]	Ora-Sweet® Ora-Sweet SF®	60[h]	60[h]
Metoprolol tartrate [62]	Tablets (50, 100)	10[a]		90[e]	90[e]
Moxifloxacin [66]	Tablets (400)	20			
Mycophenolate mofetil [67]	Capsules (250) Tablets (500)	50, 100	Ora-Sweet®	91[d]	91[d]
Naratriptan HCl [68]	Tablets (1, 2.5)	0.5	Ora-Sweet® Ora-Sweet SF®	90[e]	7[e]
Nifedipine [44]	Capsules (10, 20)	4	Ora-Sweet®	91[d]	91[d]
Norfloxacin [69]	Tablets (400)	20[b]	Strawberry syrup	56[d]	56[d]
Procainamide HCl [45,61]	Capsule/tablets (250, 375, 500)	50[a]	Ora-Sweet® Ora-Sweet SF®	60[h]	60[h]
Propylthiouracil [46]	Tablets (50)	5		91[e]	70[e]
Pyrazinamide [57]	Tablets (500)	10[a]		60[h]	60[h]
Quinidine sulphate [57]	Tablets (200, 300)	10[a]			
Rifabutin [70]	Capsules (150)	20	Ora-Sweet®	84[g]	84[g]
Rifampin [57]	Capsules (150, 300)	25[a]	Ora-Sweet® Ora-Sweet SF®	28[h]	28[h]
Sildenafil citrate [49]	Tablets (25, 50, 100)	2.5	Ora-Sweet®	91[e]	91[e]
Sotalol HCl [50,51]	Tablets (80, 120, 160, 240)	5	Ora-Sweet® Ora-Sweet SF®	91[d], 84[c] 84[c]	
Spironolactone [61,71]	Tablets (25, 50, 100)	1	Simple syrup	91[c]	91[c]
		2.5[a]	Ora-Sweet® Ora-Sweet SF®	60[h]	60[h]
Spironolactone + hydrochlorothiazide [62]	Tablets (25+25)	(5+5)[a]	Ora-Sweet® Ora-Sweet SF®	60[h]	60[h]

Drug [Ref.]	Dosage form (mg)	Suspension (mg/mL)	CMC or Ora-Plus added (1:1) of	Stability (days) in different temperatures	
				3-5°C	22-25°C
Sunitinib malate [72]	Capsules (50)	10	Ora-Sweet®	60[c]	60[c]
Tacrolimus [73-75]	Capsules (0.5, 1, 5)	0.5	Simple syrup NF	NE	56[c,e]
Terbinafine HCl [76]	Tablets (250)	25	Ora-Sweet®	42[h]	42[i]
Tetracycline HCl [57]	Capsules (250, 500)	25[a]	Ora-Sweet®	28[g]	28[h]
			Ora-Sweet SF®	10[g]	7[h]
Theophylline [77]	Capsules (125, 200, 300)	5	Ora-Sweet® Ora-Sweet SF®	NE	90[e]
Tiagabine HCl [52]	Tables (2, 4, 6, 8, 10, 12, 16)	1	Ora-Sweet®	91[d]	70[e]

a: storage in the dark, b: at fluorescent lighting, c: amber glass, d: plastic, e: amber plastic, f: polyvinyl chloride, g: polyethylene terephthalate (PET), h: amber PET; i: amber high density polyethylene bottles; NE, not evaluated; HCl, hydrochloride.
Ora-Plus® constituents: CMC-Na, citric acid, flavouring, methylparaben, microcrystalline glucose, potassium sorbate, purified water, simethicone, sodium phosphate, xanthan gum, pH 4.2. Ora-Sweet® constituents: citric acid, flavouring, glycerin, methylparaben, purified water, sodium phosphate, sorbitol, sucrose, potassium sorbate, pH 4.2. Ora-Sweet SF® constituents: citric acid, flavouring, glycerin, methylparaben, propylparaben, potassium sorbate, purified water, sodium saccharin, sodium citrate, sorbitol, xanthan gum, pH 4.2. Sugar-free.

Table 2. Stability of different drugs in oral suspension extemporaneously prepared from commercially available sodium carboxymethylcellulose (CMC-Na) in Ora-Plus® and/or other vehicle constituents.

Most of the suspensions prepared presented no substantial changes in pH, odour or physical appearance, showing that CMC-Na base usually provides products with a satisfactory safety and stability (drug content equal or superior to 90% of the original concentration) over a period of 8 weeks.

The use of Ora-Plus® extemporaneous oral suspension has provided satisfactory stability for aminophylline, cyclophosphamide, domperidone, granisetron, itraconazole, ursodiol and tramadol hydrochloride associated with acetaminophen [14,78]. However, for captopril, hydralazine hydrochloride and tetracycline hydrochloride, the suspensions were reported as not having enough stability. The problem of stability with captopril is due to its oxidative degradation, which can be solved by the addition of EDTA disodium [79]. Although, these studies are important, most of them have not evaluated the microbiological stability, an essential criterion for liquid dosage forms.

In addition to MC and CMC-Na, HPMC has also been employed in extemporaneous oral suspension. For instance, nifedipine tablets or drug powder, prepared with HPMC 1% solution in order to obtain a suspension of 1 mg/mL concentration, was stable for at least 4 weeks when stored at room or refrigerated temperatures and protected from light [80].

There is no doubt that these drug stability results are important for providing formulations for both paediatric patients and the geriatric populations that have difficulty in swallowing capsules or tablets.

3.2. Cellulose and its derivatives in oral solid dosage forms

3.2.1. Mycrocrystalline cellulose in immediate release

Microcrystalline cellulose is reported as an excipient (diluent) in oral powder and capsules extemporaneously compounded for paediatric use. Capsules and powders were prepared from commercial tablets containing 10 mg of nifedipine, which was mixed with different amounts of lactose or microcrystalline cellulose in a mortar with pestle using standard geometric dilution. Capsules were filled by a hand-operated capsule-filling machine. The oral powders and capsules containing extemporaneously prepared nifedipine showed acceptable quality regarding content uniformity, but considerable loss of the active ingredient occurred during the compounding process for both preparations. The authors demonstrated that oral powders of nifedipine (a light sensitive drug) can be replaced by capsules, which were adequately safe with either lactose monohydrate or microcrystalline cellulose as excipients for delivering a paediatric medication [81].

Recently, microcrystalline cellulose and two other common pharmaceutical excipients (starch and lactose) were investigated with regards to the choice of the best diluent for *Gymnema sylvestre* extract (a plant used as an adjuvant in the treatment of diabetes mainly in China) used to compound capsules. The *Gymnema sylvestre* extract is available as powder that presents low flowability due to its small particle size which causes problems in the filling of the hard capsules. An evaluation of these excipients was also performed in the presence of different lubricants (magnesium stearate or talc). The study showed that microcrystalline cellulose is a better diluent than lactose or starch, because it produces the most uniform particle size distribution when added to *Gymnema sylvestre* extract and also reduces the percentage of fine particles resulting in acceptable variation of the weight among the capsules (RSD< 4%). On the other hand, starch and lactose increase the number of small particles that worsen the flowability of the powder mixture. Furthermore, microcrystalline cellulose associated with 1% lubricant renders a powder mixture ready for encapsulation of *Gymnema sylvestre* extract in hard gelatin capsules, since flow agents optimize the capsule filling in the compounding routine practices [82]. The foregoing suggests that microcrystalline cellulose can be an appropriate diluent in formulating similar flowable plant extracts.

3.2.2. Cellulose ether derivatives in sustained/controlled release

3.2.2.1. Carboxymethylcellulose and hydroxypropylmethylcellulose

Some studies reveal improper use of cellulosic excipients. For example, using a high percentage (30% w/w) of CMC-Na (anionic polymer) as a diluent in the compounding of capsules of simvastatin has a deleterious effect. These capsules showed serious drug release problems in pharmaceutical tests because they did not disintegrate or dissolve at all [83]. In this case, CMC-Na should have been used as a capsule disintegrating agent at a much inferior concentration (< 6%) [12].

CMC-Na and HPMC (nonionic polymer) were evaluated by *in vitro* release studies with regards to ibuprofen (non-steroidal anti-inflammatory) extended-release from hard gelatin capsules. The study showed that different grades of CMC-Na and HPMC could control ibuprofen release to a substantial degree when used as diluents. Furthermore, the molecular weight of the polymer group that is directly related to the viscosity grade affects the drug release: the higher the molecular weight is, the slower the drug release is [40]. One year later, these researchers evaluated ibuprofen bioavailability (healthy volunteers) from hard gelatin capsules containing different grades of HPMC (K100 and K15M) and CMC-Na (low, medium, high viscosity). These capsules were prepared by filling the shells with the simple mixture of the powders (drug and polymer). The study showed that different viscosities of HPMC can modify the absorption rate of ibuprofen from hard gelatin capsules, in close correlation with a previous *in vitro* study. In particular, a higher viscosity HPMC (K15M) was a better diluent in sustained-release. On the other hand, the use of the CMC-Na with different viscosity grades did not allow for the control of the absorption rate of ibuprofen and did not correspond to *in vitro* results. However, none of the polymers seemed to have any effect on the bioavailability of the ibuprofen from hard gelatin capsules [39].

Slow-release morphine (opioid analgesic used for the relief of pain) capsules extemporaneously prepared were investigated regarding their dissolution profile. Three batches of capsules prepared by a pharmacist were compared with each other and with tablets acquired in the market. The authors describe how similar slow-release profiles were found for tablets and compounded capsules, though the latter showed a faster release-rate for morphine sulphate. Despite small variations from batch to batch, the authors describe that compounded capsules showed a remarkably consistent slow-release profile in *in vitro* studies [34].

Another study of compounded capsules containing 300 mg of morphine sulphate (a dosage unavailable in the market) reported the use of HPMC in sustained-release. There has been considerable controversy about the advisability of this practice. Release studies, performed according to the United States Pharmacopeia (USP) using a dissolution apparatus of type III, showed that almost half of the morphine was released in the first hour and that the release of the remainder was not adequately sustained. As verified in other studies, the increase of HPMC prolonged release and reduced drug release in the first hour. Other formulations prepared by placing compressed pellets in capsules showed a sustained release significantly beyond that of the pellets' original formulation. Considering that the medication can be taken after a meal, the agitation of the gastrointestinal tract would have increased, resulting in the reduction of the sustained release period and in a slight increase of the drug amount during the first hour after administration. In the first formulation, the capsules did not exhibit sustained-release that could be adequate for most applications. Formulations with a greater percentage of the HPMC are preferred. Furthermore, the pelleted formulation was superior, but it may not be feasible because it is too labour-intensive [35].

Slow-release capsules of morphine sulphate (15, 60, 200 mg) and oxycodone hydrochloride (10, 80, 200 mg) were evaluated *in vitro* by USP dissolution apparatus II. All capsules (three

batches of each) were compounded in a local pharmacy employing 40% HPMC (E4M Premium CR) and lactose as excipients and a specific machine for capsule-filling. The authors observed that the release of the active ingredients from the compounded capsules after 0.5, 4 and 12 h were less than 23%, 85% and 98%, demonstrating that HPMC is an adequate excipient for preparing slow-release capsules of morphine sulphate and oxycodone hydrochloride. The authors recommend that the ratio of active ingredient to polymer should remain constant regardless of the capsule size in order to achieve similar release rates, provided there is some degree of compression within the capsule shell. *In vitro* performance showed small intra-batch variations as well as inter-batch variations which were not statistically significant. Thus the compounding of slow release capsules yielded reproducible formulations. However, the authors mention that clinical evaluation is needed in order to determine whether the small differences are significant [37].

A variety of drugs, especially natural bioidentical hormones, have been exploited in compounding using matrix systems since 2002. Hydrophilic matrix systems were mentioned as being successfully used in slow-release capsules. The authors report that a good response of patients in a dose-related manner was observed in response to all micronized hormones administered in slow-release capsules [36].

Polymers of HPMC (K100MPRCR, K15MPRCR and E4MCR) in different proportions from 15 to 35% w/w were also used as extended-release excipients in the compounding of capsules containing 100 mg of theophylline. The polymers of HPMC were employed to prepare capsules by volumetric method for powder filling in a manual encapsulator. The extended drug release was evaluated using USP apparatus I for industrially-produced batches and for those obtained by compounding process. The dissolution profile obtained for the higher ratio (35% w/w) of HPMC (E4MCR) met USP specifications. Furthermore, reproducibility was observed with ten other compounded batches. HPMC was efficient in controlling the release of theophylline from the matrix of the capsules prepared by compounding. However, extended-release capsules containing 100 mg of theophylline (pellets) available in the market did not show prolonged release when submitted to the same test conditions [38].

To summarize, CMC-Na does not seem to be an adequate slow-releasing agent for preparing the capsules regardless of its viscosity. On the other hand, HPMC is a promising agent for prolonging the release of drugs, since it has been used before with success. The results suggest a relationship between degree of viscosity of HPMC and slow release (ibuprofen, morphine). However, reproducibility is an important requisite, and may not be assured for all formulations. In addition, studies of therapeutic efficacy are also scarce for such compounded products.

3.2.3. Cellulose ester derivatives in delayed release

Cellulose ester derivatives are used for enteric coatings of capsules, making them resistant to dissolution in low pH environments, such as the stomach, but allowing for their rapid disintegration in higher pH environments, such as the intestine. The efficiency of the coating is limited by the smooth and nonporous surface of the hard capsules. Studies into anti-

inflammatory and anti-secretory (H^+ pumps inhibitors) drugs, such as diclofenac and pantoprazole sodium salts, respectively, show that these drug formulations must be coated because they can irritate the stomach walls or degrade in acid environments [84,85].

3.2.3.1. Cellulose acetate phthalate

CAP and other agents (formaldehyde, methacrylic acid copolymer) have been used to compound delayed-release capsules of diclofenac using specific small-scale machinery or manual immersion in order to evaluate the efficiency of these enteric coating processes [32]. Capsules coated with CAP (using acetone as solvent) prepared with either small machinery or twofold manual immersion showed adequate gastro-resistance, for which the release of the drug was less than 10% in acid and greater than 75% in buffered conditions. However, the capsules coated by machinery had a poorer visual aspect than those coated by the manual process [32]. In spite of this difference, the authors did not suggest which method was the most adequate to compound delayed-release capsules of diclofenac.

A simple, quick and easily reproducible method for compounding enteric-release capsules containing diclofenac has also been described. Twenty-two batches of diclofenac sodium capsules (n=60) were divided into three groups, which were submitted to different processes of coating. A small-scale machine and an enteric coating by atomization (spraying) of organic solutions of polymers (5% CAP in a mix of acetone and alcohol) were employed for ten and six batches, respectively. Before coating, the capsules' hemi receptacles were sealed by treatment with 50% v/v hydroalcoholic solution. The dissolution test results were statistically compared inter-batch and also with reference commercial product (Voltaren® DR). Most of the batches (>75%) met the pharmacopeial requirements for enteric release, in both acid (less than 10%) and buffered (greater than 80%) conditions [33]. Results confirmed that CAP is an effective enteric coating agent in compounding practice and that the application of adequate techniques in pharmacies is important.

Delayed release capsules obtained by compounding and coating with organic solutions of CAP have been evaluated for pro-drug sodium pantoprazole, a proton pump inhibitor that undergoes degradation in the acid environment of the stomach [31,84,85]. Quality control tests were performed on capsules locally acquired in compounding pharmacies. Dissolution studies for gastro-resistance evaluation were performed with granules of pantoprazole coated with CAP and encapsulated, as well as with capsules coated with CAP or other agents (formaldehyde, shellac, methacrylic acid copolymer). However, all the samples prepared by coating with CAP (capsules or granules) released their content in an acid environment and did not show adequate gastro-resistance [31]. These results reveal the need for suitable coating techniques for compounding gastro-resistant capsules, since CAP is admittedly an effective agent for enteric coating.

4. Conclusion

Cellulose and its derivatives are very important excipients in compounded medicines. Many compounded preparations containing such excipients have been investigated since 1992,

especially for extemporaneous use; however, a great effort is still necessary in this field in order to assure quality, safety and efficacy for several other drugs. This aspect is even more relevant when these products require specific pharmaceutical features (such as delayed release) and, consequently, adequate techniques for achieving drug therapy success. It points towards the need for more research into ways to properly disseminate the appropriate use of cellulose derivatives in compounding pharmacies. A greater attention should be paid to this field because compounding is a growing practice in many countries as a result of pharmaceutical care that prioritizes the person in his/her individuality, as opposed to the average population usually targeted by companies. For all these reasons, cellulose derivatives and their applications in compounding practice were reviewed, with an emphasis on their use in solid dosage forms with modified release. Addressing the use of the cellulose derivatives, such as cellulose acetate phthalate, can be critical in the coating of capsules by hand.

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