Biolog. J. Armenia, *Special issue: Cyclodextrins*, 2001

CYCLODEXTRINS IN PHARMACEUTICAL NANOPARTICLES

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Cyclodextrins have been used in the development of pharmaceutical nanoparticles.

Poly (alkylcyanoacrylate) nanoparticles have been specially investigated, not only because of their biodegradability, but also because of the very simple polymerisation process, which occurs in aqueous medium without the presence of any polymerisation initiator. The different roles of cyclodextrins, as well as their advantage in the nanoparticle preparation, are described.

The use of newly synthesized self-assembling amphiphilic cyclodextrins in the preparation of either nanospheres or nanocapsules has also been investigated. The different cyclodextrins and the main characteristics of nanoparticles obtained are described. Due to their great variety, amphiphilic cyclodextrins seem to be promising components for the preparation of nanoparticles presenting a well-defined release rate.

Циклодекстрины использовались для создания фармацевтических наночастиц. Наночастицы поли(акрилцианоакрилат)а особенно изучены не только по их биоразрушаемости, но также из-за очень простого процесса полимеризации, что происходит в водной среде без наличия какого-либо инициатора полимеризации. Описана различная роль циклодекстринов, особенно их преимущества в производстве наночастиц.

Изучено использование новых синтезированных самосвязывающихся амфифилических циклодекстринов в изготовлении наношариков или нанокапсул. Описаны различные циклодекстрины и основные характеристики полученных наночастиц. Благодаря их большому разнообразию амфифилические циклодекстрины представляют собой перспективные компоненты для приготовления наночастиц.

Ցիկլոդեքստրինները օգտագործվել են ստեղծելու դեղագործական նանոմասնիկներ: Ուսումնասիրվել են հատկապես պոլի(ակրիլցիանոակրիլատ)ային նանոմասնիկները ոչ միայն իրենց կենսաքայքայվող ունակության, այլ նաև շատ պարզ պոլիմերիզացիայի պրոցեսի համար, որն ընթանում է ջրային միջավայրում առանց որևէ պոլիմերիզացիոն նախածեռնիչի առկայության: Նկարագրվել է ցիկլոդեքստրինների տարբեր դերը, հատկապես նրանց առավելությունը նանոմասնիկների արտադրության մեջ:

Ուսումնասիրվել է նոր սինթեզված ինքնակապվող ամֆիֆիլային ցիկլոդեքստրինների օգտագործումը նանոգնդիկների կամ նանոկապսուլների արտադրության մեջ: Նկարագրվել են տարբեր ցիկլոդեքստրիններ և տրվել են ստացված նանոմասնիկների հիմնական բնութագրերը: Շնորհիվ իրենց մեծ բազմազանության, ամֆիֆիլային ցիկլոդեքստրինները թվում են խոստումնալից կոմպոնետներ նանոմասնիկների պատրաստման համար:

Introduction

Nanoparticles (nanospheres or nanocapsules) constitute a very interesting target system for drug delivery. Because of their small size they allow a large contact surface with biological membranes and, whatever their administration route, they can significantly improve drug bioavailability. However, some drawbacks can result from the nature of the constituting polymer due to: the polymerisation process, the polymer hydrophily or lipophily, the nanoparticle loading capacity, and the drug release kinetics.

In order to overcome some of these problems, our laboratory developed the use of cyclodextrins in the preparation of nanoparticles. Two main orientations have been investigated [1]: the preparation of combined cyclodextrin/poly(alkyl cyanoacrylate) nanospheres, the preparation of amphiphilic nanoparticles.

I. Combined poly(isoalkyl cyanoacrylate)/cyclodextrin nanospheres.

Nanoparticulate systems can be prepared either by dispersion of preformed polymers or polymerisation.

Dispersion of preformed polymers concerns albumin, gelatine, alginates or synthetic polymers such as poly(lactic acid), poly(lactide-co-glycolide), poly-ε-caprolactone, or cellulose derivatives. The most frequently employed preparation methods, solvent emulsion evaporation or nanoprecipitation, allow the entrapment of highly hydrophobic drugs but require the use of organic solvents more or less toxic which implies a careful purification process.

Polymerisation methods employed in nanosphere preparation depend on the monomer type and polymerisation mechanism. However, the emulsion polymerisation is probably the most frequently employed method. Among the polymers used in such nanosphere preparation are poly(alkyl cyanoacrylates). These are particularly interesting, not only because of their biodegradability, but also because of the very simple polymerisation process which occurs in aqueous medium without the presence of any polymerisation initiator. In fact, the polymerisation process is aroused by a basic compound or more simply by the presence of hydroxyl ions resulting from water dissociation or from the presence of any kind of molecule with hydroxyl groups. One of the major drawbacks of this type of nanosphere is related to the difficulty of entrapping hydrophobic drugs which can hardly be dissolved in the aqueous polymerisation medium. We proposed the use of cyclodextrins in order to overcome this problem [2]

1.1 Preparation and characteristics of combined poly (alkyl cyanoacrylate) / cyclodextrin nanospheres.

The possibility of preparing nanospheres in the presence of cyclodextrins was investigated with poly(isobutyl cyanoacrylate) [2, 3].

Nanospheres were prepared by anionic polymerisation of isobutylcyanoacrylate in 0.01 M hydrochloric acid containing 1% w/v poloxamer 188 in the presence of α-, β-, γ-, hydroxypropyl α-, hydroxypropyl β-, hydroxypropyl γ-, and sulphobutylether β-cyclodextrin. With all the cyclodextrins it was possible to obtain nanospheres (Table 1).

Nanosphere size depends on the cyclodextrin type. The smallest particles being obtained with hydroxypropyl β- or hydroxypropyl γ-cyclodextrin were 103 and 87 nm respectively. It depends also on the cyclodextrin concentration (Table 2), an increase in cyclodextrin concentration leading to a decrease in particle size.

Table 1. Characteristics of poly(isobutyl cyanoacrylate) nanospheres prepared in the presence of cyclodextrins (5 mg/ml) and poloxamer 188 (1%). (Mean of 3 replicates ± SD; ND = not determined).

Cyclodextrin	Size (nm)	Zeta potential (mV)	Cyclodextrin content (ug CD/mg particles)
α-cyclodextrin	228 ± 69	-34.4 ± 4.0	ND
β-cyclodextrin	369 ± 7	-24.7 ± 8.2	360
γ-cyclodextrin	286 ± 9	-22.9 ± 0.6	240
hydroxypropyl α-cyclodextrin	244 ± 25	-27.0 ± 2.2	ND
hydroxypropyl β-cyclodextrin	103 ± 6	-8.6 ± 0.9	247
hydroxypropyl γ-cyclodextrin	87 ± 3	-2.6 ± 2.2	220
sulphobutyl ether β-cyclodextrin	319 ± 10	-45.4 ± 2.4	ND

Table 2. Influence of the cyclodextrin concentration on characteristics of poly(isobutyl cyanoacrylate) nanospheres.

Cyclodextrin	Concentration (mM)	Size (nm)
sulphobutyl ether β-cyclodextrin	5	252
	10	196
	15	171
	20	126
hydroxypropyl γ-cyclodextrin	5	64
	10	53
	15	46

It is interesting to note the role played by cyclodextrins. Not only, their concentration influences the particle size, but the amount of cyclodextrin combined to the nanospheres and measured by the method of Vikmon [4] represents about 1/4 to 1/3 of the nanosphere weight (Table 1). Furthermore, their influence on the ζ potential of the particle, which is about – 40 mV in the absence of cyclodextrin increases to values close to zero in the presence of neutral natural cyclodextrins or their hydroxypropyl derivatives. In the presence of the negatively charged sulphobutyl ether of β-cyclodextrin, it decreases to – 45 mV (Table 1).

These results suggest an influence of cyclodextrins on nanosphere formation, either by initiation of the polymerisation process of alkyl cyanoacrylate or by steric stabilization of the nanospheres.

Normally, the anionic polymerisation starts with the monomer activation by nucleophile groups, such as weak bases or hydroxyl ions from the water dissociation, present in the polymerisation medium. In the present case, the numerous hydroxyl groups of cyclodextrins could behave like polymerisation initiators. However, further studies have shown that nanospheres prepared by nanoprecipitation [5] of either: 1) the product obtained by dissolution in acetonitrile of combined poly(alkyl cyanoacrylate)/hydroxypropyl β-cyclodextrin nanospheres or 2) the poly(alky cyanoacrylate) alone, do not present any difference in their infrared spectra [3, 6], and that infrared spectra of the supernatant of 1) is comparable to that of hydroxypropyl β-cyclodextrin, indicating a high hydroxypropyl β-cyclodextrin concentration in the supernatant. This study leads to the conclusion that there are no covalent bonds between the hydroxypropyl β-cyclodextrin and the polymer chains. The mechanism by which cyclodextrins could initiate the alkyl cyanoacrylate polymerisation is not clearly demonstrated and is disputable.

The alkyl cyanoacrylate polymerisation occurs inside the surfactant (poloxamer 188) micelles and ends with the disappearance of monomers from polymerisation medium, and

with a concomitant release of the surfactant. Normally, the surfactant adsorption at the nanosphere surface results in their steric stabilization. However, in the present case investigations carried out on nanospheres prepared in the presence of hydroxypropyl β-cyclodextrin showed that the presence of poloxamer does not affect the particle size which decreases (from 300 to 50 nm) with an increase in hydroxypropyl β-cyclodextrin concentration (from 0 to 12.5 mg/ml) in the polymerisation medium [3, 6]. Similarly the zeta potential of the particles decreases from a high negative value (– 40 mV) to a value close to 0 mV with an increase in hydroxypropyl β-cyclodextrin concentration, and ζ potential values are not affected by the presence of poloxamer 188 [3]. These results, associated to the high amount of cyclodextrins combined to the nanospheres, leads to the conclusion that cyclodextrins have a steric stabilization effect on poly(alkyl cyanoacrylate) nanospheres.

1.2 Combined poly (alkyl cyanoacrylate) / cyclodextrin nanospheres loaded with active ingredients.

Nanospheres of poly(isobutyl cyanoacrylate) were loaded with a series of steroids (model molecules) [3, 6, 7] and nanospheres of poly(isohexyl cyanoacrylate) were loaded with saquinavir [8]. The loading was carried out by addition of the active ingredient free or included in hydroxypropyl β-cyclodextrin to the polymerisation medium, and the nanospheres were recovered by freeze-drying.

In the case of steroids, except for spironolactone, the nanospheres obtained with the hydroxypropyl β-cyclodextrin inclusions have a smaller diameter (about 100 nm) than the nanospheres obtained with the free steroids (between 200 and 300 nm) (Table 3).

Table 3. Characteristics of steroid-containing poly(isobutyl cyanoacrylate) nanospheres prepared with (+) and without (-) hydroxypropyl β-cyclodextrin. (Mean of 3 replicates ± SD).

Steroid	Size (nm)		Drug loading (μmol/g)		Loading increase (fold number)
(presence of CD)	-	+	-	+	
Hydrocortisone	281 ± 7.5	105 ± 3.5	6.0	2.2	7
Prednisolone	271 ± 3	115 ± 26.5	0.33	43.0	130
Spironolactone	263 ± 7.5	294 ± 4	18.4	127.2	7
Testosterone	216 ± 16	110 ± 6	7.9	67.6	8.5
Megestrol acetate	249 ± 18	93 ± 3.5	0.65	3.6	5.5
Danazol	255 ± 19	100 ± 19	1.0	33.2	33
Progesterone	268 ± 25.5	92 ± 12	2.5	69.6	28

In the presence of hydroxypropyl β-cyclodextrin, a significant increase in loading capacity of nanospheres is observed, varying from 7 times for spironolactone to 130 times for prednisolone.

Physical state of progesterone in combined poly(isobutyl cyanoacrylate)/hydroxypropyl β-cyclodextrin nanospheres was investigated by differential scanning calorimetry and compared with the separate products [3, 6]. In the nanospheres, it is possible to observe the disappearance of the endothermic peak (130 °C) characteristic of progesterone melting, and its replacement by a broad endothermic transition in the region 130-170 °C. This indicates that progesterone is either molecularly dispersed in the nanospheres or, at least, in amorphous state.

The in vitro release of progesterone, studied in alkaline borate buffer of pH = 8.4, occurs with a very fast initial release followed by a much slower release phase reaching a plateau after 30 h. The release rate is faster and higher for small particles than for large ones

(35% in the second phase for particles of 150 nm diameter, and 62% for particles of 70 nm). In the presence of esterases, the progesterone release is almost total after 1 or 2 h depending on the particle size [3, 6]. For its part, hydroxypropyl β-cyclodextrin was totally released in less than 1 h [3].

Loading of nanospheres, which is dramatically increased in the presence of hydroxypropyl β-cyclodextrin, could be explain by three mechanisms. The inclusion compound steroid/hydroxypropyl β-cyclodextrin can be absorbed at the nanosphere surface; this phenomenon corresponds to the steroid fast release observed in the in vitro dissolution tests. On the other hand, the inclusion could be entrapped in the nanosphere core during their formation by polymerisation. However, due to the high hydrophily of the external part of the inclusion compound, this mechanism does not seem to be predominant and may not occur at all. Finally, in the aqueous polymerisation medium, the inclusion dissociates in free species, according to its stability constant:

steroid/ hydroxypropyl β-cyclodextrin ⇔ steroid + hydroxypropyl β-cyclodextrin

The inclusion compound dissociation could be accelerated by capture of the free steroid by the hydrophobic polymer during its formation. In order to verify this hypothesis, a correlation was looked at between the nanosphere loading capacity and the polymer/water partition coefficient in the presence or not of hydroxypropyl β-cyclodextrin and for various steroid concentrations [3, 7]. In fact the value of the partition coefficient polymer/water was replaced by that of the partition coefficient octanol/water, because there is a linear relationship between these two values:

$$\log P(\text{polymer/water}) = a \times \log P(\text{octanol/water}) + b$$

In the presence or not of hydroxypropyl β-cyclodextrin the partition coefficient is not the main factor influencing nanosphere loading. On the other hand, the product of the initial concentration in active ingredient and the partition coefficient is the determining factor of the loading. This result indicates that, in the absence of cyclodextrins, the steroid affinity for the polymer is not sufficient to result in noticeable nanosphere loading.

In conclusion, the active ingredient, free or included in the cyclodextrin, is partly adsorbed at the nanosphere surface; this localisation corresponds to its fast release. The active ingredient is also entrapped in the nanosphere core; this localisation corresponds to the plateau observed in the absence of esterases.

2. Amphiphilic cyclodextrin nanoparticles

Natural cyclodextrins, as well as their hydrophilic derivatives, despite their prominent advantage of being powerful drug solubilizers, have the major inconvenience of their high external hydrophily, which reduces the possibility of interactions with biological membranes. For this reason, several types of amphiphilic cyclodextrin have recently been synthesized [9]. These cyclodextrin derivatives differ not only by the position and length of the substituents, but also by the nature of the chemical bond between the substituent and the cyclodextrin.

The work we carried out was mainly oriented towards the "skirt-shaped" cyclodextrins substituted by esterification (O) on the secondary hydroxyl groups (II) [10, 11]. In a second attempt, we investigated the influence of the chemical bond nature, the chain length and the

substitution localisation. With these amphiphilic cyclodextrins it has been possible to prepare either nanospheres or nanocapsules.

2.1 Preparation and characteristics of skirt-shaped cyclodextrin nanospheres.

Skirt-shaped α- or β-cyclodextrins with hydrocarbon chains from C_6 to C_{14}, which have surfactant characteristics [12], can very easily lead to nanospheres.

Nanospheres of skirt-shaped cyclodextrins can be prepared by different methods: nanoprecipitation [13, 14], the most simple, or emulsion solvent evaporation [15]. The nanoprecipitation method consists in dissolving the amphiphilic cyclodextrin in an organic solvent miscible in water (acetone or absolute ethanol) and injecting this solution in an aqueous phase, with or without surfactant, under stirring. Cyclodextrins precipitate spontaneously and form nanospheres. The organic solvent, and part of the water, are removed by evaporation under vacuum to give the desired concentration in nanosphere suspension.

Nanospheres present very good sphericity and narrow dispersity, even without the presence of surfactant [13] (Table 4). Their size is not affected by stirring rate, but is increased with an increase in ionic surfactant concentration, and is independent of the non-ionic surfactant concentration [13] (Table 5).

Table 4. Characteristics of skirt-shaped β-cyclodextrin nanospheres prepared by nanoprecipitation in the presence or not of surfactant. Influence of the hydrocarbon chain length. (PI: polydispersity index)

Surfactant	βCD- C_6(II,O)		βCD- C_{12}(II,O)		βCD- C_{14}(II,O)	
	Size (nm)	PI	Size (nm)	PI	Size (nm)	PI
(none)	107 ± 17	0.045	103 ± 12	0.032	89 ± 26	0.093
PEF68	103 ± 14	0.096	106 ± 17	0.069	98 ± 16	0.048
Span® 85	120 ± 31	0.072	101 ± 19	0.075	100 ± 18	0.076

Table 5. Characteristics of skirt-shaped β-cyclodextrin nanospheres prepared by nanoprecipitation in the presence or not of surfactant. Influence of nature and concentration in surfactant. (PI: polydispersity index; Pluronic® F68: PEF68; SDS : sodium dodecyl sulphate; BZD^+: benzethonium chloride)

Surfactant (%w/v)	PEF68		SDS		BZD^+	
	Size (nm)	PI	Size (nm)	PI	Size (nm)	PI
-	100 ± 13	0.05	100 ± 13	0.05	100 ± 13	0.05
0.055	103 ± 17	0.03	136 ± 33	0.11	135 ± 54	0.088
0.156	100 ± 23	0.04	140 ± 24	0.032	159 ±34	0.1
0.257	105 ± 14	0.01	139 ± 26	0.018	173 ± 29	0.079

Nanospheres were loaded with either hydrophilic or lipophilic drugs. The encapsulation of doxorubicin hydrochloride in skirt-shaped cyclodextrin (C_6) nanospheres [16, 17] requires the presence of a surfactant in the nanoprecipitation medium. In the presence of poloxamer, the concentration in doxorubicin in nanospheres is high (40% w/w), and the nanospheres are stable in saline buffer medium, however they do not resist aqueous dilution. In the presence of sodium dodecyl sulphate, doxorubicin concentration in the nanospheres is much lower (7% w/w), and the nanospheres, which resist to aqueous dilution are not stable in saline buffer medium. The optimal fixation is obtained by diluting the nanosphere suspension prepared with sodium dodecyl sulphate, by an equivalent amount of poloxamer solution [16, 17].

More interestingly, skirt-shaped γ-cyclodextrin (C_6) nanospheres were loaded with lipophilic drugs: progesterone, testosterone and hydrocortisone, the loading being carried out in the presence of Pluronic F68 either during the nanoprecipitation process or on blank nanospheres. The drug concentration in nanospheres depends on the affinity constant of the drug for the parent cyclodextrin cavity, and depends inversely on the drug water solubility (Table 6).

Table 6. Influence of drug characteristics on the loading capacity of γ-cyclodextrin diester (C_6) nanospheres prepared by nanoprecipitation.

Drug	Loading capacity (μg/mg)	Water solubility (μg/ml)	KγCD
Progesterone	60-80	3.3	24.000
Testosterone	20-30	23.0	16.500
Hydrocortisone	< 15	326.0	2.240

When nanospheres are loaded with progesterone [14], the loading capacity varies with the initial content of drug in the preparation medium, and reaches an optimum corresponding to almost 100% of entrapment efficiency (Table 7).

Table 7. Influence of the initial progesterone content (mg/30 mg amphiphilic cyclodextrin) on the loading capacity and the diameter of skirt-shaped γ-cyclodextrin (C_6) nanospheres prepared by nanoprecipitation in the presence of Pluronic F68

Drug content m g/30 mg γCD-C_6(II,O)	Drug loading		Entrapment	Size
	(%)	(mg/mg γCD-C_6(II,O))	(%)	(nm)
0.5	49.09 ± 10.0	11.5 ± 3.75	71.0 ± 22.09	126 ± 44
1.0	74.91 ± 20.5	24.12 ± 8.65	73.09 ± 26.22	125 ± 44
2.5	91.96 ± 0.92	81.19 ± 15.05	97.81 ± 18.1	118 ± 21
5.0	91.06 ± 0.4	75.07 ± 20.26	45.04 ± 12.13	122 ± 25
10.0	89.15 ± 0.52	80.98 ± 21.82	24.29 ± 6.54	113 ± 28
20.0	97.19 ± 3.09	53.01 ± 1.10	7.50 ± 0.15	121 ± 19

Differential scanning calorimetry studies showed the disappearance of the endothermic melting peak of progesterone at 130 °C in the nanospheres. On X-ray diffraction patterns, peaks characteristic of the amphiphilic γ-cyclodextrin diester are recovered in the unloaded and loaded nanospheres. However, no signal corresponding to progesterone crystalline domains is detected in the loaded nanospheres [14].

The progesterone is very rapidly released in vitro and reaches an equilibrium depending on the nature of the dissolution medium and on the affinity of the drug for this medium. There is no influence of the formulation parameters. Such a fast release profile is of interest when an improvement in the bioavailability of the drug is desired [14]. These results suggest that progesterone is associated molecularly on the surface of nanospheres and not matrix encapsulated. This association probably occurs through hydrophobic interactions at specific sites of the carrier. The possibility of inclusion of the drug in the cyclodextrin cavity is not excluded [14].

2.2 *Preparation and characteristics of skirt-shaped cyclodextrin nanocapsules*

Nanocapsules of cyclodextrin diesters were prepared by a method very similar to the nanoprecipitation of nanospheres [18]. A lipophilic phase, constituted either of Miglyol 812® or benzyl benzoate and the amphiphilic β-cyclodextrin derivative (with either C_6, C_{12}

or C_{14} hydrocarbon chains) is dissolved in acetone and added under mechanical stirring to an aqueous phase with or without surfactant (Pluronic ® PEF68). The nanocapsules are formed immediately, and acetone is removed by evaporation under vacuum together with part of the water to obtain a suspension of the desired concentration. Nanocapsules loading is obtained by adding the drug to the organic phase.

Nanocapsules characterized by transmission electron microscopy and electron microscopy after freeze-fracture present a diameter close to 200 nm and have a low polydispersity index (Table 8) [18].

Table 8. Characteristics of β-cyclodextrin diester nanocapsules containing benzyl benzoate. Influence of the hydrocarbon chain length (PI: polydispersity index)

Surfactant	βCD- C_6(II,O)		βCD- C_{12}(II,O)		βCD- C_{14}(II,O)	
	Size (nm)	PI	Size (nm)	PI	Size (nm)	PI
PEF68	204 ± 49	0.083	183 ± 48	0.057	178 ± 15	0.130
Span® 85	256 ± 66	0.040	223 ± 49	0.001	213 ± 43	0.029

Nanocapsules were loaded either with indomethacin, progesterone or amphotericin B as drug models. The encapsulation yield is 90% or more [19] (Table 9).

Table 9. Encapsulation of various drugs in β-cyclodextrin diester nanocapsules (C_6) containing benzyl benzoate.

Drug	Drug encapsulation yield (%)	Drug content (% w/w)
Indomethacin	90	21.6
Progesterone	>98	7.5
Amphotericin B	90	11

The rat gastric ulcerative effect of indomethacin encapsulated was compared with that of an indomethacin solution (Indocid®). Whatever the administered dose (5 or 10 mg/kg), the ulcerative effect is significantly decreased, without disappearance of the bioavailability of the product [19]. The protection afforded by the encapsulated indomethacin is 82% for 5 mg/kg and 53% for 10 mg/kg administered.

2.3 Preparation and characteristics of amphiphilic cyclodextrin nanocapsules

A series of amphiphilic β-cyclodextrins was prepared, varying by: the substitution localisation: on the primary (I) or the secondary (II) face, the hydrocarbon chain length (C_6 and C_{14}) branched (B) or not, and the bond type (ester: -O, or amide: -N) [20, 21] (Table 10).

Table 10. Physico-chemical properties of amphiphilic β-cyclodextrins (* with decomposition).

Amphiphilic cyclodextrin	Molecular weight (g/mol)	Melting point (°C)	Solubility in ethanol		Solubility in acetone		HLB calculated
			(mM)	(mg/ml)	(mM)	(mg/ml)	
βCD- C_6(II,O)	2506	230	0.6	1.5	1.0	2.5	8.9
βCD- C_6(I,O)	1820	250*	2.0	3.6	2.0	3.6	11.1
βCD- C_6(I,N)	1813	224	1.0	1.8	0.4	0.72	11.2
βCD- C_6B(I,N)	1813	309*	0.2	0.36	0.8	1.44	11.2
βCD- C_{14}(I,N)	2597	198	0.4	1.04	0.54	1.04	7.8

Nanocapsules were prepared using either acetone or ethanol as organic phase [21]. Results obtained with ethanol are presented in Tables 11 and 12.

Table 11. Mean diameter (nm) of amphiphilic cyclodextrin nanocapsules obtained in ethanol as a function of the cyclodextrin molar concentration

Amphiphilic cyclodextrin	Molar CD concentration					
	0.1	0.2	0.4	0.6	0.8	1
βCD- C_6(II,O)	435	763	998			
βCD- C_6(I,O)	399	385	405	430	532	579
βCD- C_6(I,N)	285	279	284	315	307	367
βCD- C_6B(I,N)	305	391	546	583	767	
βCD- C_{14}(I,N)	332	351	883			

Table 12. Polydispersity index of amphiphilic cyclodextrin nanocapsules obtained in ethanol as a function of the cyclodextrin molar concentration

Amphiphilic cyclodextrin	Molar CD concentration					
	0.1	0.2	0.4	0.6	0.8	1
βCD- C_6(II,O)	0.09	0.24	1.20	1.50		
βCD- C_6(I,O)	0.47	0.49	0.53	0.65	0.68	0.70
βCD- C_6(I,N)	0.09	0.21	0.14	0.21	0.15	0.16
βCD- C_6B(I,N)	0.15	0.38	0.79		0.86	
βCD- C_{14}(I,N)	0.24	0.11	0.65			

In the light of this work, it appears that substitution of cyclodextrins on the primary face results in more appropriate nanocapsule forming agents in the sense that monodispersity can be better achieved with these cyclodextrin derivatives. The length of aliphatic chain grafted to the molecule and bond type used in the grafting play important roles in determining the physico-chemical properties of the products. Optimum chain length was linear C_6, with either deoxy or amido bond. Molecules with branched substituents tend to collapse at high concentrations, because of their probably larger surface area, while long aliphatic chain substitution or substitution on the secondary face resulted in instable nanocapsules.

Conclusion. Our laboratory has developed studies on the use of cyclodextrins in modern pharmaceutical dosage forms, among which nanoparticles.

It appears that cyclodextrins and their hydrophilic derivatives can be very useful agents in the preparation and loading of polymer nanoparticles, and specially poly(akyl cycanoacrylate) nanoparticles. Cyclodextrins, not only, act as polymer initiators, steric stabilizing agents but also they significantly increase the nanoparticle loading capacity. It can be assumed that, depending on their nature and concentration, it will be possible to modulate not only the nanoparticle load but also the release kinetic of the active ingredient.

Finally, amphiphilic cyclodextrins represent a new series of surface-active agents capable of self-association to lead either to nanospheres or to nanocapsules. Due to their potential variety, it will be possible to prepare nanoparticles specially tailored to obtain a defined release rate for a given active ingredient.

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