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Formulation and *in-vitro* drug release for β-cyclodextrin nanosphears using emulsification solvent-evaporation method

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Abstract

This study gives information about the formulation of β-cylcodextrin nanosphere by emulsification solvent-evaporation method based on emulsifying an organic phase containing the β-cylcodextrin in an aqueous phase of pluronic-F68 as surfactant. The nanospheres are loaded with hydrophobic drug and the *in-vitro* drug release study was conducted. The formulation of colloidal particle was associated with amphiphilic properties of the β-cylcodextrin derivatives. However, the partitioning of the β-cyclodextrin between the organic and aqueous phases is always depends on the concentration of the surfactant. In the case of nanospheres loaded with Irinotican hydrochloride, the partitioning of the drug occurs between the dispersed phase containing β-cylcodextrin and the continuous aqueous phase containing pluronic-F68.

***Keywords**:* Amphiphilic cyclodextrins; Emulsification; Solvent-evaporation method; Nanospheres; Irinotecan; Surfactant; Pluronic-F68.

Introduction

Targeted drug delivery system is a drug-loaded vehicle to deliver the required amount of drug to the targeted site for necessary period both efficiently and precisely. Different carrier materials are being constantly developed to overcome the undesirable properties of drug molecules (Bodmeier and Chen, 1990). Amongst them β-cylcodextrin have been found as potential candidates because of the ability to alter physical, chemical and biological properties of guest molecules through the formation of inclusion complexes (Allemann *et al*., 1992; Kataoka *et al*., 1993). They provide a number of potential sites for chemical modification. Different cavity sizes of β-cylcodextrin makes the drug to entrap in different molecular dimensions and the microenvironment in their cavity is relatively non-polar and lipophilic (Allemann *et al*., 1993; Fessi *et al*., 1988). They have a good aqueous solubility, low toxicity and high thermal stability. They protect the conjugated drugs from biodegradation.

Amphiphillic and hydrophobic esters of cyclodextrins obtained by the introduction of fatty acid chain into the secondary face of the natural molecule have been used to prepare colloidal nanospheres, which are considered as promising carriers for hydrophobic drugs. In this method β-cylcodextrin molecule previously dissolved in a water miscible organic solvent when the later is injected into an aqueous phase. The hydrophobic drug is usually added to the organic phase of the formulation.

β-cylcodextrin increases the aqueous solubility of many poorly soluble drug with a good enhancement effect in bioavailability. Prevention of incompatibility and improvement of stability is the major advantage (Lemo-senna *et al*., 1998). Irinotecan hydrochloride is a semi-synthetic derivative of Camptothecin, an Alkaloid inhibits Topoisomarase-1 which is soluble in methanol or water. β-cyclodextrin molecules previously dissolved in a water miscible organic solvent when the latter is injected into an aqueous phase (Al-Saden *et al*., 1982; Jeffery *et al*., 1991). The hydrophobic drug is added to the organic phase of the formulation.

In Emulsification solvent-evaporation method the hydrophobic drugs in polymeric matrices, involves the emulsification of water immiscible

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organic solutions of preformed polymers in aqueous phases containing soluble surfactants (Bodmeier and McGinity, 1987a & 1987b). However, in order to obtain nanospheres, the modifications of emulsification procedure have been applied, such as the salting-out process and high- pressure emulsification procedure, or Emulsification solvent diffusion.

Materials and methods

Beta cyclodextrin obtained from Sigma Aldrich; Irinotecan hydrochloride from Shilpa health care Pvt.Ltd; Pluronic-F68 was purchased in Signet Corporation. The other chemicals were of Pharmaceutical or reagent grades from same labs.

Nanosphere preparation

Irinotecan Hydrochloride Trihydrite loaded nanospheres were prepared by emulsification solvent evaporation method. Briefly, β cyclodextrin (60 mg) and the drug Irinotican (20mg) were dissolved in methylene chloride (2.4ml). This solution was dispersed in an aqueous phase (117.6ml) containing Pluronic-F68 using probe sonicater for 3 minutes. Thereafter organic solvent was evaporated by mechanical stirring (600 rpm) for 8 hours at room temperature and filtered in a 0.8 μm membrane (AA, Millipore).

Pre-formulation

Drug-polymer compatibility study: IR spectra for Irinotican hydrochloride and β-cyclodextrin were taken in KBr pellets using Perkin-Elmer Fourier Transform infrared spectrophotometer with following scan parameters: scan range 500-3000cm-1; number of scan 16; resolution 4.0cm^{-1} ;unit%T.

In vitro release Kinetic studies: The suspension of drug-loaded nanospheres were packed inside the dialysis membrane (Hi-media135) and suspended in 500ml of phosphate buffer with pH 7.5 in dissolution apparatus with USP specification.

Results and Discussion

A significant number of studies have suggested that nanospheres made were being of useful drug delivery especially for targeted drug delivery system. Entrapping drugs into nanospheres was shown to be enhanced bioavailability and efficacies. Like most molecules of its class, Irinotecan hydrochloride has poor water solubility. In order to overcome this problem drug-cyclodextrin is made. In this work, we evaluated the feasibility of β-cyclodextrin nanospheres preparation by emulsification solvent evaporation method. According to the microsphere preparation manufacturing process, the emulsification methods involve a sequences of complex interfacial phenomena in which numerous parameters can affect the preparation path way and the physicochemical properties of the final nanospheres. These parameters include the type of organic solvent or solvent mixture the solvent/polymer/non-solvent interaction, the nature of emulsifying agent and the rate of solvent evaporation.

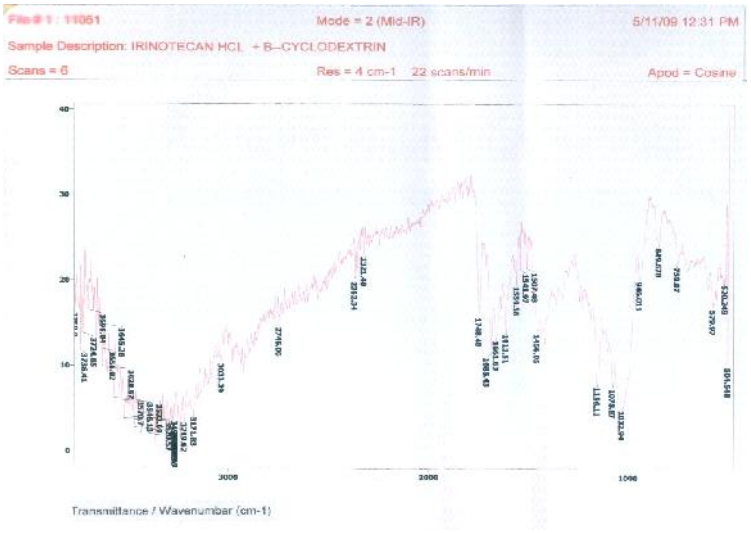

Fig.1. FT – IR for Irinotecan

Infra red studies of drug and polymer

The FT-IR compatibility between the polymer β-cyclodextrin with Irinotecan hydrochloride shows better compatibility. The spectral study

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reveals that a strong peak at 3570cm-1, and C-H stretching vibration disappeared (Fig.1 & 2).

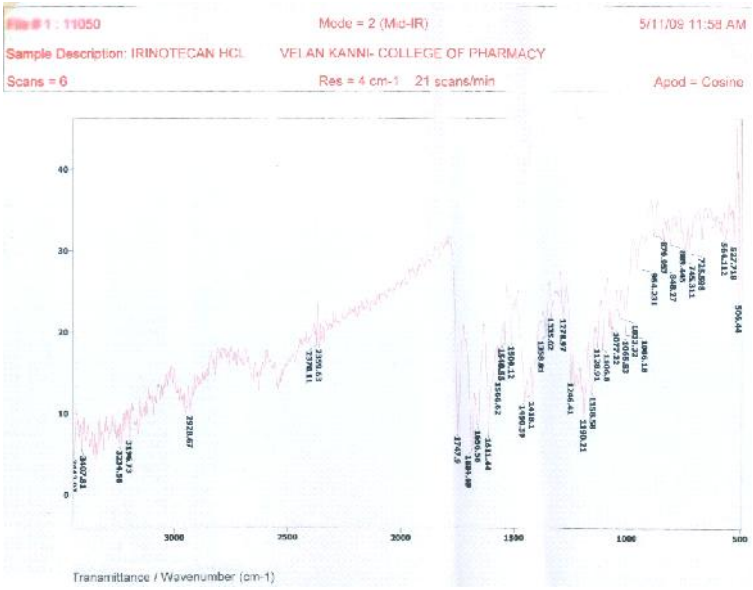

Fig. 2. FT - IR for Irinotecan with β-Cyclodextrin

Table 1. In-vitro drug release data for Irinotecan hydrochloride for 24 hours

Time	Drug release (mg/ml)	%	Claim
15 minutes	0.26 mg/ml	1.3%	20 mg/ml
30 minutes	0.34 mg/ml	1.7%	
45 minutes	0.24 mg/ml	1.21%	
1 hour	0.31 mg/ml	1.6%	
2 hours	0.45 mg/ml	2.26%	
4 hours	0.62 mg/ml	3.1%	
8 hours	0.78 mg/ml	3.9%	
10 hours	1.23 mg/ml	6.16%	
12 hours	1.26 mg/ml	6.3%	
14 hours	1.27 mg/ml	6.36%	
16 hours	1.15 mg/ml	5.75%	
18 hours	2.15 mg/ml	10.75%	
20 hours	2.67 mg/ml	13.35%	
24 hours	3.15 mg/ml	15.75%	

In-Vitro release kinetics

The *in-vitro* release profile of Irinotecan hydrochloride was obtained by representing the percentage of release with respect to the amount of Irinotecan loaded in nanospheres. The Irinotecan loaded nano capsule exhibits a sustained release effect. In 24hrs, it gives the release of 79.45% (Table 1). The nanospheres of β-cyclodextrin with Irinotecan hydrochloride complex shows better drug release about 24 hours.

Conclusion

In this study, it is possible to prepare β-cyclodextrin nanosphere with Irinotecan hydrochloride using the emulsification evaporation method. The formation of the inclusion compounds greatly modified the physical and chemical properties of the guest molecule, mostly in terms of water solubility. This is the reason why β-cyclodextrin has attracted much interested in pharmaceutical application: because inclusion of compound β-cyclodextrin with hydrophobic molecule is able to penetrate the body tissue, this used to biologically active compounds under specific conditions. Nanospheres drug delivery systems gives better drug delivery with reduced toxicological effects. The capacity of the nanospheres to associate with a hydrophobic drug shows the best-sustained drug delivery pattern in emulsification solvent evaporation method.

References

1. Allemann E, Gurny R and Doelker E (1992) Preparation of aqueous polymeric nanodispersions by a reversible salting out process: influence of process parameters on particle size. *Int. J.Pharm*., 87, 247-253.
2. Allemann E, Leroux JC, Gurny R and Doelker E (1993) In vitro extended-release properties of drug-loaded poly(DL-Lactide Acid) nanospheress produced by salting-out procedure. *Pharm. Res*., 10, 1732-1737.
3. Al-Saden AA, Whateley TL and Florence AT (1982) Polaxamer Association in aqueous solution. *J.Colloid Interface Sci*., 90, 303-309.
4. Bodmeier R and Chen H 1990 Indomethacin polymeric nanosupensions prepared by microfluidization. *J. Controlled Release*, 12, 223-233.
5. Bodmeier R and McGinity JW (1987a) Polyactide acid mircospheres containing quinidine base and quinidine sulphate prepared by slovent evaporation techniquie. I.Method and morphology. *J.Microencapsulation*, 4, 279-288.
6. Bodmeier R and McGinity JW (1987b) Polylactide acid microspheres containing quinidine base and quinidine

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sulphate prepared by slovent evaporation techniquie. II. Some processes parameters influencing the preparation and properties of microspheres. *J.Microencapsulation,* 4, 289-297.

7. Fessi H, Puisieux F and Devissaguet JP (1988) Procede de preparation de systems colloidaux dispersibles d'une substance sous forme de nanospheres. US Patent no.5118, 528.
8. Jeffery H, Davis SS and O'Hagan (1991) The preparation and characterisation of poly(lactide-co-glycolide) microparticles. I: Oil-in-water emulsion solvent evaporation. *Int. J.Pharm*., 77, 169-175.
9. Kataoka K, Kwon G, Yokoyama M, Okano T, Sakurai Y (1993) Block copolymer micelles as vehicles for drug delivery. *J.Controlled Release*, 24, 119-132.
10. Lemo-senna E, Wouessidejewe D, Lesieur S, Puisieux F, Couarraze G and Duchene D (1998) Evaluation of the hydrophobic drug loading characteristics in nanopreciptated amphiphilic cyclodextrins nanosphere. *Pharm. Develop Tech*, 3, 85-94.