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Research Article

COMPATIBILITY STUDIES OF CAMPTOTHECIN WITH VARIOUS PHARMACEUTICAL EXCIPIENTS USED IN THE DEVELOPMENT OF NANOPARTICLE FORMULATION

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ABSTRACT

Objective: For the design and development of any novel formulation, assessment of drug - excipients compatibility using different techniques such as thermal and isothermal stress testing, represents an important phase in preformulation stage. The potential physical and chemical interactions between the drug and excipients can affect the chemical nature, stability, bioavailability of drugs and subsequently, affects their therapeutic efficacy and safety.

Method: To assess the drug – excipients compatibility, the analytical techniques like Differential Scanning Calorimetry (DSC), Fourier Transform Infrared Spectroscopy (FTIR) and Isothermal Stress Testing (IST) were adopted. In the present study, the possible interaction between the Camptothecin with Eudragit S 100, β Cyclodextrin and Poloxamer 188 were evaluated initially by DSC. The drug and each excipient (1:1 w/w) were stored at 40 ± 2°C and 75 ± 5 % RH for 1 month.

Results: The FTIR spectrum of pure drug, excipients and drug - excipients mixtures were compared to find out the possible interaction. Stressed binary mixtures (stored at 50°C for 2 weeks) were periodically examined for any change in colour and the drug content was determined quantitatively using HPLC. No concrete evidence of interaction was observed between drug and the excipients.

Conclusion: On the basis of the results obtained from DSC, FTIR and IST studies, all the excipients used were found to be compatible with the drug and can be used for the development of Nanoparticles formulation.

Keywords: Camptothecin, Compatibility, DSC, FTIR, IST, HPLC.

INTRODUCTION

The development of pharmaceutical formulation requires a previous knowledge of physicochemical properties of drug and excipients. The excipients are known to facilitate administration and modulate the release of active component and are considered to be pharmaceutically inert, but physical and chemical interactions with active components are possible [1]. Drug – excipients compatibility studies lays a foundation in careful selection of most appropriate excipients and helps in designing a chemically stable and effective dosage form [2, 3]

Camptothecin (CPT) is a naturally occurring cytotoxic alkaloid isolated from the Chinese plant *Camptotheca accuminata* [4, 5]. CPT has shown a broad spectrum of antitumor activity against various tumours by inhibiting the activity of DNA topoisomerase [4, 6-8]. Unfortunately, poor pharmaceutical profile, with extreme aqueous insolubility, low stability of the lactone form at physiological pH, and severe systemic toxicities hinder the clinical application of CPT [9]. Recently, specifically designed dosage forms and techniques for camptothecin have been evaluated to overcome their hydrophobic and unstable characteristics.

In recent years, nanostructured materials such as nanoparticles [10] have been considered as potential carriers for hydrophobic drug delivery that may resolve the aforementioned problems [11].

Nanoparticles have become an important area of research in the field of drug delivery because they have the ability to deliver a wide range of drugs to varying areas of the body for sustained periods of time. In recent years, significant research has been done using nanoparticles as oral drug delivery vehicles [12]. Polymeric nanoparticles are actively investigated as drug carriers to reduce drug toxicity and degradation, so as to deliver therapeutic agents to several sites of action and to promote a suitable, selective and specific targeted therapy [13]

Assessment of possible incompatibility between the drug and excipients is an important part of preformulation [14]. Incompatibility between drug and excipients can affect the chemical nature, stability and bioavailability of drug and subsequently affects their therapeutic efficacy and safety [15, 16]. Drug – excipients compatibility testing at an early stage helps in selection of excipients that increase the probability of developing a stable dosage form [16]. Despite the importance of the issue, there is no universal accepted protocol for drug-excipients incompatibility testing [16, 17].

Differential Scanning Calorimetry is widely used thermal technique in drug excipients compatibility assessment. However, the interpretation of the thermal data is not always easy and, to avoid misinterpretations and misleading of thermal analysis results, it must be emphasized that the interactions observed at high temperatures may not always be relevant under ambient conditions [18-20].

Therefore, the use of analytical technique such as Fourier Transform Infrared (FTIR) Spectroscopy is another approach used in compatibility tests based on the hypothesis that same functional group change during drug-excipients interaction [18, 21, 22]. Another method that is commonly employed for evaluating the drug excipients compatibility is Isothermal Stress Testing (IST). This method involves storing the drug-excipients blend with or without moisture at high temperature. IST has specific application in pharmaceutical industry where the interaction between drug and excipients is visually observed and the drug content is determined quantitatively using HPLC [17, 23 - 25].

The purpose of the present investigation was to evaluate the compatibility of camptothecin with various pharmaceutical excipients to be used in the nanoparticle formulations utilizing the different analytical techniques such as differential scanning calorimetry, Fourier Transform Infrared Spectroscopy and Isothermal stress testing.

MATERIALS AND METHODS

Camptothecin was purchased from S.M Herbals, India. β Cyclodextrin and Poloxamer (Grade 188) were procured from sigma Aldrich, India. Eudragit S 100 was obtained from Evonik Industries, India. All other chemicals and reagents used were of analytical grade.

Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry (DSC-60, Shimadzu, Japan) was used for thermal analysis of drug and mixture of drug and excipients in a 1:1 w/w ratio [25]. Individual samples (drug and excipients) as well as physical mixture of drug and excipients were weighed to about 5mg in DSC aluminium pan [16]. The sample pan was crimped for effective heat conduction and scanned in the temperature range of 50-300°C [26]. Heating rate of 20°C min^{-1} was used and the thermogram obtained was reviewed for evidence of any interactions [27, 28].

Fourier Transform Infrared Spectroscopy (FT-IR)

FT-IR spectra's were recorded on a FTIR spectroscopy using the instrument Shimadzu FT-IR 8400S in the frequency range of 400-4000 cm^{-1} with the resolution of 4 cm^{-1} using potassium bromide discs method [16, 25]. The drug and each selected excipients (1:1 w/w) were stored at 40 ± 2°C and 75 ± 5 % RH for 1 month [28]. Individual samples as well as the mixture of drug and excipients were ground, mixed thoroughly with potassium bromide for 3-5mins in a mortar and compressed into disc by applying a pressure of 5 tons for 5 mins in hydraulic press. The concentration of sample in potassium bromide should be in the range of 0.2% to 1% [29]. The pellets were placed in light path and spectrum was obtained and reviewed for evidence of any interactions [30].

Isothrmal stress testing

In the IST studies, the drug and excipients were individually weighed in 10ml glass vial and mixed on a vortex mixer for 2mins, each vials was sealed using a Teflon-lined screw cap and stored at 50°C (Hot Air Oven, Technico, India) for 2 weeks [31]. The samples were periodically examined for any unusual colour change. After 2 weeks of storage at the above conditions, samples were quantitatively analyzed using HPLC [16, 32].

HPLC analysis

To the each vial containing the samples, 2ml of methanol was added. The mixture was vortexed and transferred to 100ml volumetric flask. Vials were rinsed with methanol to make up the volume in volumetric flask [16]. The samples were centrifuged and the supernatant was filtered through 0.45 µm nylon membrane filters [27]. After dilution, samples were analyzed using HPLC and the drug content is determined from the calibration curve prepared within the expected range [32].

For the analysis of drug-excipients mixtures, Shimadzu HPLC system was used with the best chromatographic conditions equipped with C18 column (ODS 250 mm X 4.6 mm with 5 micron pore size, Phenomenax) using a mobile phase combination of 0.5% W/V of Ammonium Acetate aqueous solution and acetonitrile (85:15, v/v) in an isocratic mode elution with a flow rate of 1mL min^{-1} at the column oven temperature of 35°C and the samples were analyzed by PDA detector at a wavelength of 368 nm [33, 34].

RESULTS AND DISCUSSION

Differential scanning calorimetry

The DSC thermogram corresponding to Camptothecin, β – cyclodextrin and the complex are shown in figure 1. Camptothecin exhibits a characteristic endothermic peak at 260.44°C corresponding to its melting temperature. A broad endothermic band from 60 - 120°C was observed for the amorphous β – cyclodextrin, which was related to loss of water molecules i.e., dehydration process [35]. The DSC thermogram for the solid complex of Camptothecin and β – cyclodextrin showed an endothermic peak at 263.77°C associated with the formation of inclusion complex in the solid state. As such there is no interaction between Camptothecin and β – cyclodextrin.

DSC thermogram of Camptothecin, Eudragit S 100 and binary mixture of Camptothecin and Eudragit S 100 are shown in figure 2. In the thermogram, the drug showed a sharp endothermic peak at 260.44°C, corresponding to the melting temperature. The DSC thermogram of physical mixture of drug and polymer the characteristic endothermic peak of drug was observed at 262.12°C. Thus, changes in the melting endotherm of the drug from 260.44 to 262.12°C could be due to the mixing of the drug and excipients, which lower the purity of each component in the mixture [27]. The results showed that there is no interaction between the Camptothecin and eudragit S 100.

The DSC thermogram of Camptothecin, Poloxamer 188 and physical mixture of Camptothecin and Poloxamer 188 are shown in figure 3. The sharp endothermic peak of Camptothecin was observed at 260.44°C corresponding to its melting point. The physical mixture of Camptothecin and Poloxamer 188 on the other hand showed an apparent endothermic peak of Camptothecin at 262.45°C. It can be concluded that there is no interaction between the Camptothecin and Poloxamer 188.

fourier tranform infrared spectroscopy (FT-IR)

The use of FTIR technique allows, pointing out the implication of the different functional groups of guest and host molecules by analyzing the significant changes in the shape and position of the absorbance bands.

The principle absorption peak of camptothecin showed a – OH stretching at 3,425.7 cm^{-1}, ester stretching 1,736 cm^{-1}, C=O stretching at 1,648 cm^{-1}, pyridone, C=C and C–N stretching at 1,597, 1,572, and1,436 $cm^{-1}$and C–C(=O)–O stretching at 1,148 cm^{-1} respectively. Peak at 767 cm^{-1} appears to be a contribution of four adjacent hydrogen bonds on hetero-aromatic nucleus (table 1).

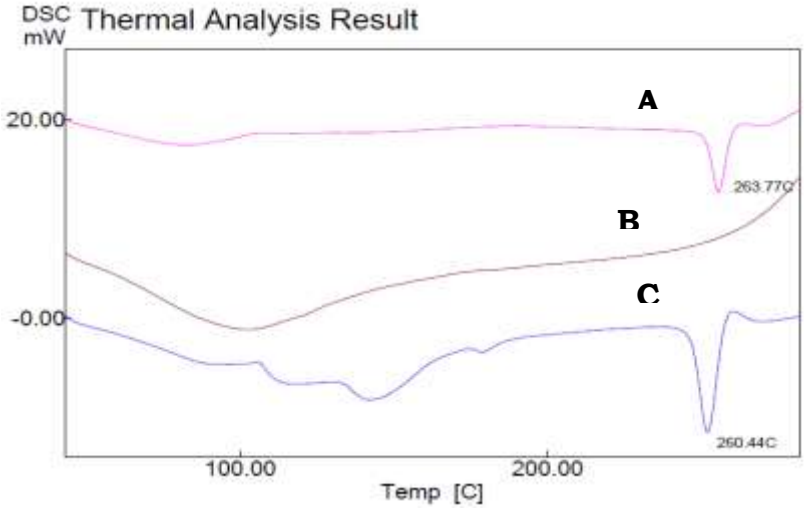


Fig. 1: It shows DSC thermogram of (A) Pure Camptothecin, (B) Pure β – cyclodextrin and (C) Physical mixture of Camptothecin and β – cyclodextrin.

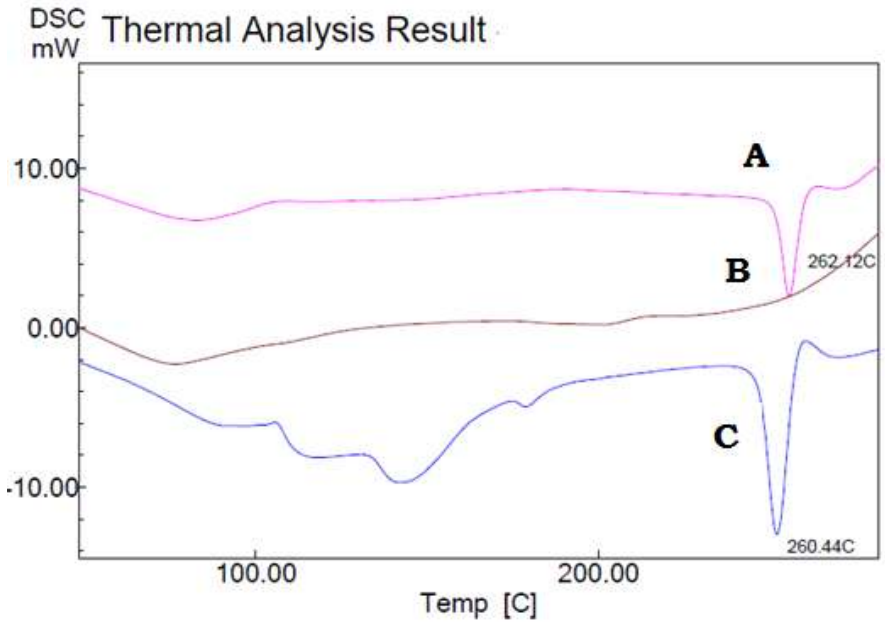


Fig. 2: It shows DSC thermogram of (A) Pure Camptothecin, (B) Pure Eudragit S 100 and (C) Physical mixture of Camptothecin and Eudragit S 100.

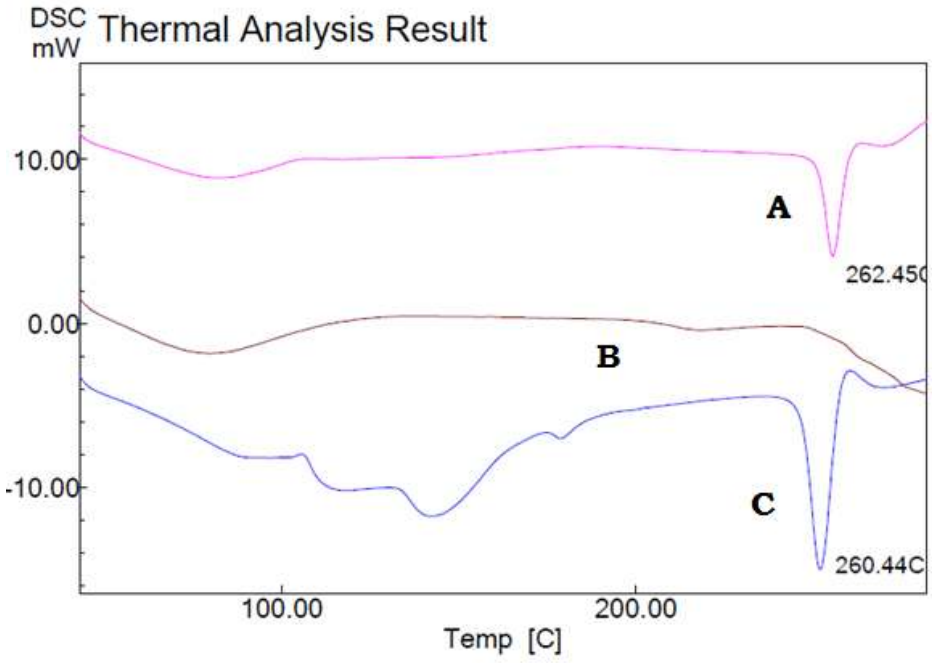


Fig. 3: It shows DSC thermogram of (A) Pure Camptothecin, (B) Pure Poloxamer 188 and (C) Physical mixture of Camptothecin and Poloxamer 188.

Table 1: It shows FTIR spectroscopy data of Camptothecin and β Cyclodextrin

S. No	F.G	Standard (cm^{-1})	CPT (cm^{-1})	F.G	Standard (cm^{-1})	β - CD (cm^{-1})	F.G	CPT + β - CD (cm^{-1})
1	OH	3600-3400	3432.47	OH	3400-3600	3385.33	OH	3429.16
2	ester	1740-1730	1740.62	CH_2	2930-2920	2924.04	ester	1740.56
3	C=O	1655-1645	1652.57	C-H	1370-1350	1368.18	C=O	1652.76
4	C=C	1610-1550	1580.30	C-O	1320-1000	1157.33	C=C	1580.54
5	C=N	1450-1350	1438.42	C-O	1320-1000	1080.45	C=N	1438.07
6	C–O	1320-1000	1157.27	C-H	1050-900	947.25	C–O	1157.17

F.G: Functional Group, β – CD: β cyclodextrin

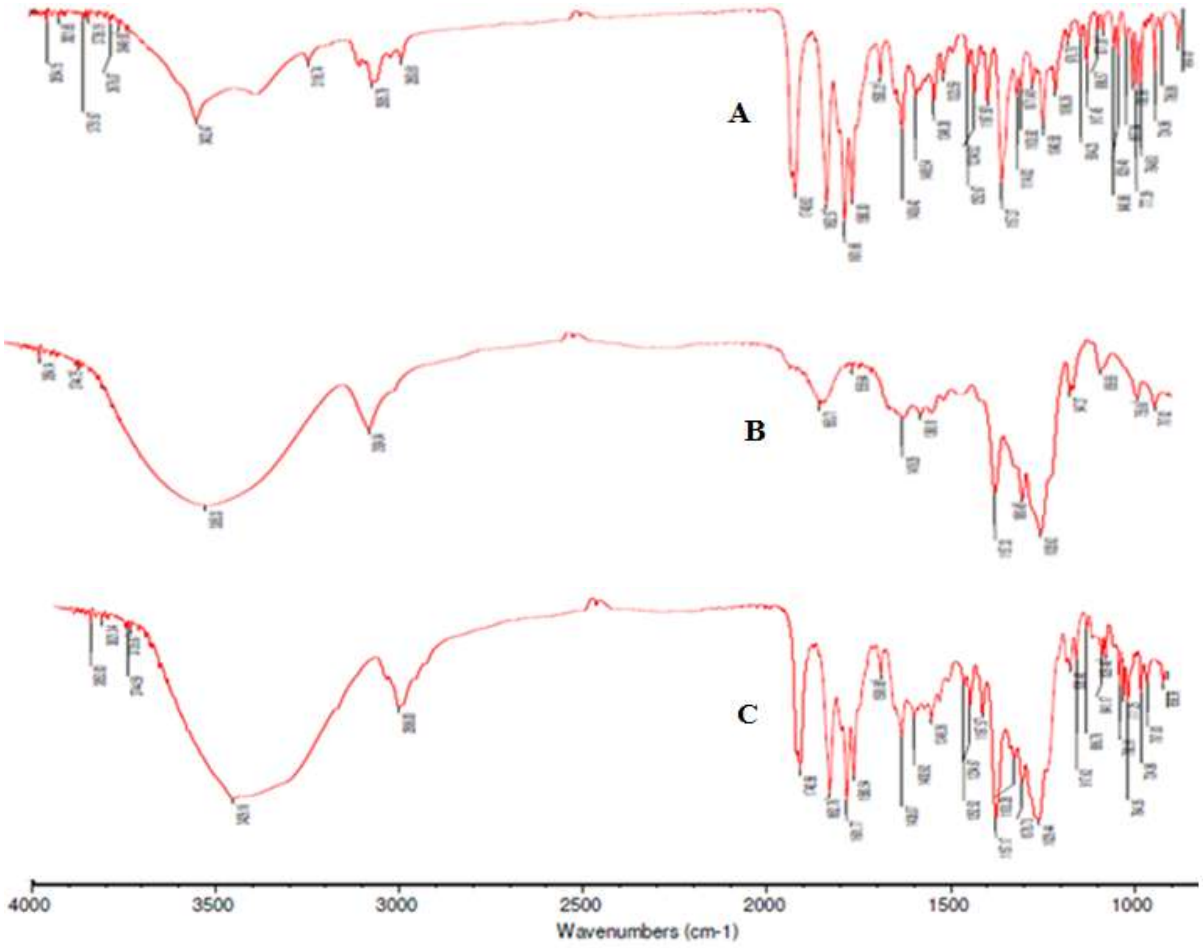
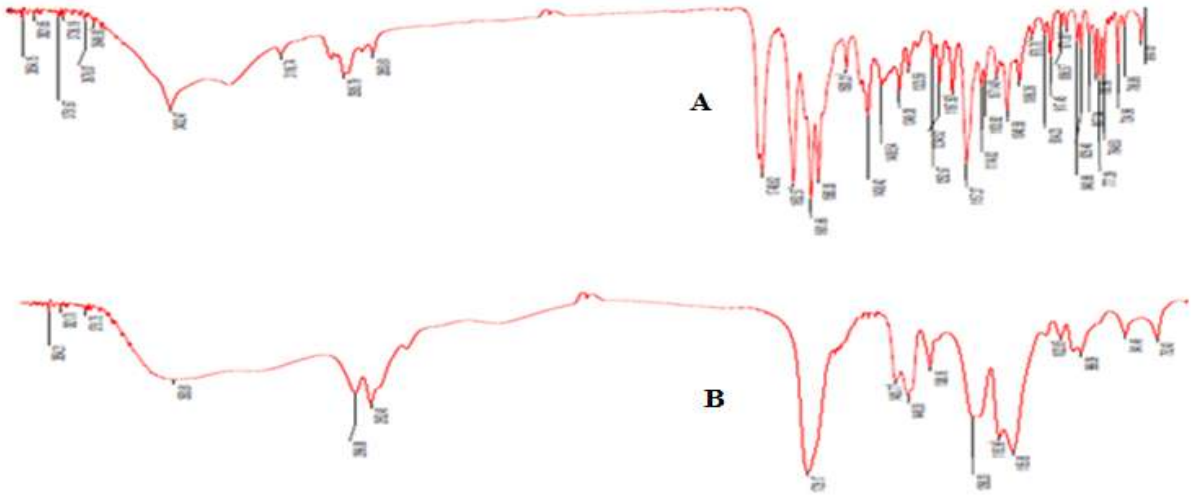


Fig. 4: It shows FTIR spectrum of (A) Pure Camptothecin, (B) Pure β Cyclodextrin and (C) Mixture of Camptothecin with β Cyclodextrin

The FTIR spectra of Camptothecin, β cyclodextrin and mixture of Camptothecin with β cyclodextrin are shown in Figure 4. In the FTIR spectrum of β – CD, the absorption band with maximum of 3385.33 and 2926 cm^{-1} were observed. It belongs to O-H group and the valence vibrations of the C-H bonds in the CH and CH_2 groups. In the region of 1368.18 cm^{-1} the absorption bands was due to deformation vibrations of the C-H bonds in the primary and secondary hydroxyl groups of β - CD and absorption bands in the region of 1157.33 $cm^{-1}$and 1080.45 cm^{-1} corresponds to the valence vibrations of the C-H bonds in the ether and hydroxyl groups respectively. The absorption bands in the region 950 - 700 cm^{-1} belong to the deformation vibrations of the C-H bonds and the pulsation vibrations in glucopyranose cycle. The physical mixture of Camptothecin and β-CD showed no change in the position of the bands at 3429.16 (-OH), 1740.56 (ester), 1652.76 (C=O), 1580.54 (C=C), 1438.07 (C=N) and 1157.17 (C-O) respectively indicating no interactions between Camptothecin and β-cyclodextrin (table 1).



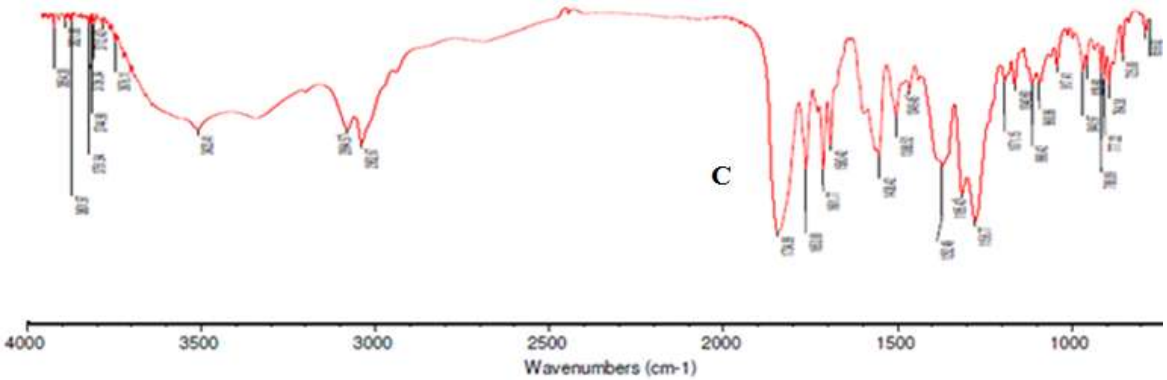


Fig. 5: It shows FTIR spectrum of (A) Pure Camptothecin, (B) Pure Eudragit S 100 and (C) Mixture of Camptothecin with Eudragit S 100

Table 2: It shows FTIR spectroscopy data of Camptothecin and Eudragit S 100

S. No	F.G	Standard (cm^{-1})	CPT (cm^{-1})	F.G	Standard (cm^{-1})	Eu S 100 (cm^{-1})	F.G	CPT + Eu S 100 (cm^{-1})
1	OH	3600-3400	3432.47	OH	3400-2800	2952.48	OH	3433.41
2	Ester	1740-1730	1740.62	C=O	1730-1720	1729.17	ester	1734.89
3	C=O	1655-1645	1652.57	$-CH_3$	1500-1400	1449.30	C=O	1653.00
4	C=C	1610-1550	1580.30				C=C	1580.42
5	C=N	1450-1350	1438.42				C=N	1438.42
6	C–O	1320-1000	1157.27				C–O	1156.77

F.G: Functional Group, Eu S 100: Eudragit S 100

The FTIR spectra of Camptothecin, Eudragit S 100 and mixture of Camptothecin with Eudragit S 100 are shown in Figure 5. FTIR spectrum of Eudragit S-100 showed the absorption peak at 2952.48 cm^{-1} due to presence of O–H (carboxylic acid), at 1729.17 cm^{-1} due to the presence of C = O (ester) and at 1449.30 cm^{-1} due to $-CH_3$ bend.

The Physical mixture of Camptothecin and Eudragit S 100 showed no change in the position of the bands at 3433.41 (-OH), 1734.89 (ester), 1653.00 (C=O), 1580.42 (C=C), 1438.42 (C=N) and 1156.77 (C-O) respectively indicating no interactions between Camptothecin and Eudragit S 100 (table 2).

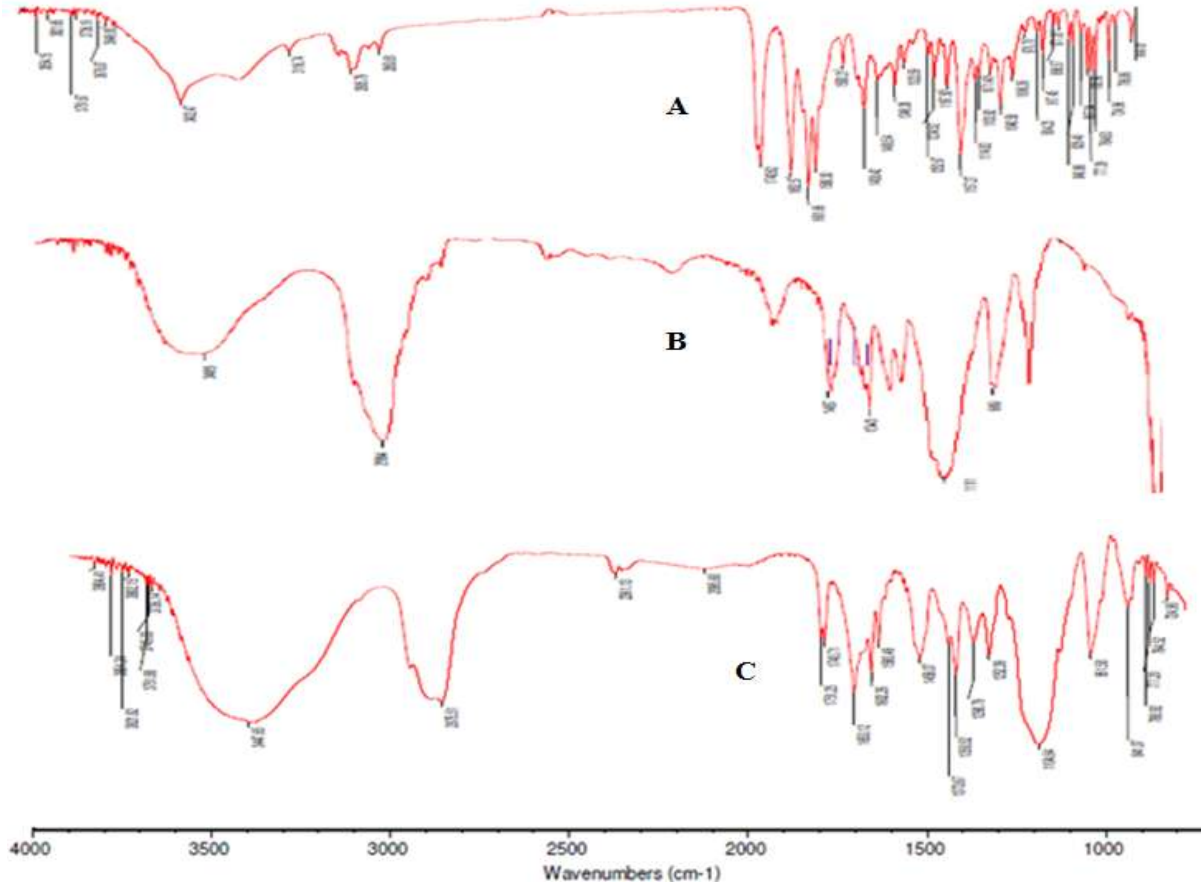


Fig. 6: It shows FTIR spectrum of (A) Pure Camptothecin, (B) Pure Poloxamer 188 and (C) Mixture of Camptothecin with Poloxamer 188.

Table 3: It shows FTIR spectroscopy data of Camptothecin and Poloxamer 188

S. No	F.G	Standard (cm^{-1})	CPT (cm^{-1})	F.G	Standard (cm^{-1})	P188 (cm^{-1})	F.G	CPT + P188 (cm^{-1})
1	OH	3600-3400	3432.47	OH	3600-3400	3485	OH	3447.65
2	Ester	1740-1730	1740.62	CH	3000-2850	2884	ester	1740.71
3	C=O	1655-1645	1652.57	OH	1350-1000	1343	C=O	1653.12
4	C=C	1610-1550	1580.30	C-O	1150-1070	1111	C=C	1580.49
5	C=N	1450-1350	1438.42				C=N	1458.07
6	C–O	1320-1000	1157.27				C–O	1157.64

F.G: Functional Group, P188: Poloxamer 188

The FTIR spectra of Camptothecin, Poloxamer 188 and mixture of Camptothecin with Poloxamer 188 are shown in Figure 6. The FTIR spectrum of poloxamer 188 was characterized by principal absorption peaks at 3485 cm^{-1} (O-H, stretch, broad), 2884 cm^{-1} (C-H stretch aliphatic), 1343 cm^{-1} (in plane O-H bend) and 1111 cm^{-1} (C–O stretch). The Physical mixture of Camptothecin and Poloxamer showed no change in the position of the bands at 3447.65 (-OH), 1740.71 (ester), 1653.12 (C=O), 1580.49 (C=C), 1458.07 (C=N) and 1157.64 (C-O) respectively. The result shows that there are no interactions between Camptothecin and Poloxamer 188 (table 3).

Isothermal Stress Testing (IST)

In the Isothermal stress testing, the drug and polymer mixture was physically observed at different time intervals. No characteristic colour change was observed. Assay value was observed using HPLC from the samples of drug polymer mixtures stored at 50° C for 2 weeks. The assay of the drug polymer mixtures were found good was within the acceptable range (table 4). This clearly indicates the stable nature of the camptothecin with β-cyclodextrin, Eudragit S 100 and Poloxamer 188.

Table 4: It shows drug content of Camptothecin after storage at 50 °C for 2 weeks.

Time	Drug + β-Cyclodextrin	Drug + Eudragit S 100	Drug + Poloxamer 188
50 °C for 2 weeks	105.11	99.55	99.17

CONCLUSION

The compatibility of camptothecin with various excipients was studied by different analytical techniques like Differential Scanning Calorimetry, Fourier Transform Infrared Spectroscopy and Isothermal Stress Testing. However, techniques such as FTIR and isothermal stress testing techniques after storage of the mixture of camptothecin and individual excipients under stressed conditions should be taken in conjunction with DSC results to reach any definite conclusion.

In the present study, results of DSC along with FTIR and HPLC (for IST) were successfully employed to assess the compatibility of camptothecin with the excipients. No concrete evidence of interaction was observed between camptothecin and the excipients like β cyclodextrin, Eudragit S 100 and Poloxamer 188. No characteristic colour change was observed during the storage at 50 °C for 2 weeks. The HPLC analysis results of this mixture evident the chemical stability of Camptothecin as the assay was within the acceptable range. Hence, this data's attests the potentiality of the excipients for the successful development of a nanoparticle formulation.

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REFERENCE

1. Lira AM, Araujo AAS, Basilio IDJ, Santos BLL, Santana DP, Macedoc RO. Compatibility studies of lapachol with pharmaceutical excipients for the development of topical formulations. Thermochimica Acta 2007; 457: 1–6.
2. Pandian P, Kannan K, Manikandan M, Manavalan R. Formulation and evaluation of oseltamivir phosphate capsules. Int J Pharm Pharm Sci 2012; 4 (4): 342-347.
3. Aulton ME. Pharmaceutics The scientific principles of dosage form design. 2nd ed: Churchill Livingstone; 2002.
4. Wall ME, Wani MC, Cook CE, Palmer KH, Mcphail AT, Sim GA. Plant antitumor agents I. The isolation and structure of camptothecin, a novel alkaloidal leukemia and tumor inhibitor from *Camptotheca acuminate*. J Am Chem Soc 1966; 88: 3888–3890.
5. Masato Watanabe, Kumi Kawano, Masayuki Yokoyama, Praneet Opanasopit, Teruo Okanoc, Yoshie Maitani. Preparation of camptothecin-loaded polymeric micelles and evaluation of their incorporation and circulation stability. Int J Pharm 2006; 308: 183–189.
6. Giovanella BC, Hinz HR, Kozielski AJ, Stehlin Jr JS, Silber R, Potmesil M. Complete growth inhibition of human cancer xenografts in nude mice by treatment with 20-(S)-camptothecin. Cancer Res 1991; 51: 3052–3055.
7. Potmesil M. Camptothecins: from bench research to hospital wards. Cancer Res 1994; 54: 1431–1439.
8. Merisko-Liversidge E, Sarpotdar P, Bruno J, Hajj S, Wei L, Peltier N, Rake J, Shaw JM, Pugh S, Polin L, Jones J, Corbett T, Cooper E, Liversidge GG. Formulation and antitumor activity evaluation of nanocrystalline suspensions of poorly soluble anticancer drugs. Pharm Res 1996; 13: 272–278.
9. Pablo Botella, Ibane Abasolo, Yolanda Fernandez, Carlos Muniesa, Sonia Miranda, Manuel Quesada, Jorge Ruiz, Simo Schwartz Jr., Avelino Corma. Surface-modified silica nanoparticles for tumor-targeted delivery of Camptothecin and its biological evaluation. J Controlled Release 2011; 156(2): 246–257.
10. Vargas A, Pegaz B, Debefve E, Konan-Kouakou Y, Lange N, Ballini JP. Improved photodynamic activity of porphyrin loaded into nanoparticles: an in vivo evaluation using chick embryos. Int J Pharm 2004; 286(1–2): 131–145.
11. Cheng-Liang Peng, Ping-Shan Lai, Feng-Huei Lin, Steven Yueh-Hsiu Wu, Ming-Jium Shieh. Dual chemotherapy and photodynamic therapy in an HT-29 human colon cancer xenograft model using SN-38-loaded chlorin-core star block copolymer micelles. Biomaterials 2009; 30: 3614–3625.
12. Hans ML, Lowman AM. Biodegradable nanoparticles for drug delivery and targeting. Curr Opin Solid State Mater Sci 2002; 6: 319–327.
13. Anna Valeria Vergoni, Giovanni Tosi, Raffaella Tacchi, Maria Angela Vandelli, Alfio Bertolini, Luca Costantino. Nanoparticles as drug delivery agents specific for CNS: in vivo biodistribution. Nanomedicine: NBM 2009; 5: 369–377.
14. Sonali S. Bharate, Sandip B. Bharateb, Amrita N. Bajaj. Interactions and incompatibilities of pharmaceutical excipients with active pharmaceutical ingredients: a comprehensive review. J Excipients and Food Chem 2010; 1(3): 3-26.

15. Rowe RC, Sheskey PJ, Quinn ME. Handbook of Pharmaceutical Excipients. 6th Ed: Pharmaceutical Press: London; 2009.
16. Rajan K. Verma, Sanjay Garg. Selection of excipients for extended release formulations of glipizide through drug – excipient compatibility testing. J Pharm Biomed Anal 2005; 38: 633–644.
17. Serajuddin ATM, Thakur AB, Ghoshal RN, Fakes MG, Ranadive SA, Morris KR, Varia SA. Selection of solid dosage form composition through drug-excipient compatibility testing. J Pharm Sci 1999; 88: 696–704.
18. Marini A, Berbenni V, Moioli S, Bruni G, Cofrancesco P, Margheritis C, Villa M. Drug-excipient compatibility studies by physico-chemical techniques: the case of Indomethacin. Journal of Thermal Analysis and Calorimetry 2003; 73: 529–545.
19. Macedo RO, Gomes do Nascimento T, Veras JWE. Compatibility and stability studies of propranolol hydrochloride binary mixtures and tablets for TG and DSC-photovisual. Journal of Thermal Analysis and Calorimetry 2002; 67: 483–489.
20. Bogdan Tit, Adriana Fulias, Geza Bandurb, Eleonora Marianc, Dumitru Tit. Compatibility study between ketoprofen and pharmaceutical excipients used in solid dosage forms. J Pharm Biomed Anal 2011; 56: 221– 227.
21. Joshi BV, Patil VB, Pokharkar VB. Compatibility studies between carbamazepine and tablet excipients using thermal and non-thermal methods. Drug Dev Ind Pharm 2002; 28: 687–694.
22. Monajjemzadeh F, Hassanzadeh D, Valizadeh H, Siahi-Shadbad MR, Mojarrad JS, Robertson T, Roberts MS. Assessment of feasibility of Maillard reaction between baclofen and lactose by liquid chromatography and tandem mass spectrometry, application to pre formulation studies. AAPS Pharm Sci Tech 2009; 649–656.
23. Kandarapu R, Grover V, Chawla HPS, Garg S. Evaluation of the compatibility of ketorolac tromethamine with selected polymers and common tablet excipients by thermal and isothermal stress testing. STP Pharma Sciences 2001; 11: 449–457.
24. Gu L, Strickley RG, Chi LH, Chowhan ZT. Drug-excipient incompatibility studies of the dipeptide angiotensin-converting enzyme inhibitor, moexipril hydrochloride: dry powder vs wet granulation. Pharma Research 1990; 7: 379–383.
25. Farnaz Monajjemzadeh, Davoud Hassanzadeh, Hadi Valizadeh, Mohammad R. Siahi-Shadbad, Javid Shahbazi Mojarrad, Thomas A. Robertson, Michael S. Roberts. Compatibility studies of acyclovir and lactose in physical mixtures and commercial tablets. Eur Journal of Pharm Biopharm 2009; 73: 404–413.
26. Tatsuyoshi Wakasawa, Kyoko Sano, Yutaka Hirakura, Toshimasa Toyooka, Satoshi Kitamura. Solid-state compatibility studies using a high-throughput and automated forced degradation system. Int J Pharm 2008; 355: 164–173.
27. Nihar Ranjan Pani, Lila Kanta Nath, Sujata Acharya. Compatibility studies of nateglinide with excipients in immediate release tablets. Acta Pharm 2011; 61: 237–247.
28. Sibel Bozdag Pehlivan, Birsel Subasi, Imran Vural, Nursen Unlu and Yilmaz capan. Evaluation of drug-excipient interaction in the formulation of celecoxib tablets. Acta Poloniae Pharmaceutica - Drug Research 2011; 68(3): 423-433.
29. Santanu Mallik, Mahendra D. Kshirsagar, Vipin Saini. Studies on physical/chemical compatibility between synthetic and herbal drugs with various pharmaceutical excipients. Der Pharmacia Lettre 2011; 3(5): 173-178.
30. Afsar C. Shaikh, Sayyed Nazim, Shaikh Siraj, Tarique Khan, Siddik Patel M, Mohammad Zameeruddin, Arshad Shaikh. Formulation and Evaluation of Sustained Release Tablets of Aceclofenac using Hydrophilic Matrix System. Int J Pharm Pharm Sci 2011; 3(2): 145-148.
31. Narayana Raju P, Prakash K, Lakshmi Narasu M. Compatibility Study of Lamivudine with Various Cellulose Polymers. E-Journal of Chemistry 2009; 6(S1): S17-S20.
32. Choudhury PK, Murthy PN, Tripathy NK, Panigrahi R, Behera S. Investigation of Drug Polymer Compatibility: Formulation and Characterization of Metronidazole Microspheres for Colonic Delivery. Webmedcentral 2012; 1-20.
33. Shahe Mahammad S, Madhusudhana Chetty, Ramana Murthy KV. Preformulation Studies of Quetiapine Fumarate. Journal of Pharmacy Research 2012; 5(1): 672-677.
34. Karin Liltorp, Trine Gorm Larsenb, Birgitte Willumsenb, Rene Holma. Solid state compatibility studies with tablet excipients using non thermal Methods. J Pharm Biomed Anal 2011; 55: 424–428.
35. Hoda A. El-Maradny, Sana A. Mortada, Ola A. Kamel, Ahmed H. Hikal. Characterization of ternary complexes of meloxicam-HPβCD and PVP or L-arginine prepared by the spray-drying technique. Acta Pharm 2008; 58: 455–466.