



Characterization of Drug and Polymers for Development of Colon Specific Drug Delivery System

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ABSTRACT

To dosage form design characterization of drug and polymers is an important aspect. The objective of this work was to characterize Capecitabine, natural polymers like, guar gum, xanthan gum, chitosan and other excipients. As a part of characterization studies of Capecitabine, Differential scanning calorimetry (DSC) was used to investigate thermal effects and nature of drug, supported by X-ray powder diffraction (X-RPD), showed two endothermic peaks and indicated crystalline nature of the drug. Scanning electron microphotographs (SEM) was used to study surface topography. Fourier - transform infrared (FT-IR), solubility study, flowability studies of drug and excipients were carried out as part of characterization. Solubility studies at different pH showed feasibility of drug at any pH. Drug excipient interaction studies carried out which shows there was no chemical interaction between the drug and the polymers. Stability of bulk drug at accelerated conditions was determined, good stability was observed.

Key words: Characterization, DSC, X-RPD, Capecitabine, Polymers, Stability.

1. INTRODUCTION:

Colon targeting is advantageous in treating diseases of colon (irritable bowel syndrome, inflammatory bowel disease, including Chron's disease and ulcerative colitis), oral delivery of proteins and peptides where a delay in systemic absorption is therapeutically desirable (nocturnal asthma, arthritis, angina).^{1,2} For the past five decades scientific data collectively known as characterization or preformulation studies have been developed for supporting the dosage form design of a new drug and its quality control.^{3,4} Capecitabine, the first oral fluoropyrimidine derivative of 5-fluorouracil and is widely used in the treatment of metastatic colorectal and breast cancer. It is a pro-drug that is converted to fluorouracil in the body tissues following the oral administration. It is readily absorbed from the gastrointestinal tract, as drug is freely available at any pH and hence judicious selection of release retarding system like drug in matrix is necessary. The recommended daily dose is large i.e., 2.5 gm/m² and has a short elimination half-life of 0.5-1 h^[5]. Xanthan gum is a high molecular weight extracellular heteropolysaccharide, produced by fermentation with the gram-negative bacterium *xanthomonas campestris*. The primary structure of this naturally produced cellulose derivative contains a cellulosic backbone β -D-glucose residues and a trisaccharide side chain of β -D-mannose- β -D-glucuronic acid- α -D-mannose attached with alternate glucose residues of the main chain^[6,7]. Guar gum is a polysaccharide derived from the seeds of *Cyamopsis tetragonolobus*, family Leguminosae. It consists of linear chains of (1 \rightarrow 4)- β -D-mannopyranosyl units with α -D-galactopyranosyl units attached by (1 \rightarrow 6) linkages^[8]. Chitosan is a hydrophilic, biocompatible and biodegradable polysaccharide of low toxicity which in recent years has been used for development of drug delivery systems. It has been exploited for the preparation of microspheres for controlled release systems. Small chitosan microspheres were also developed for site specific delivery of anticancer agents, such as oxantrazole and 5-fluorouracil^[9,10].

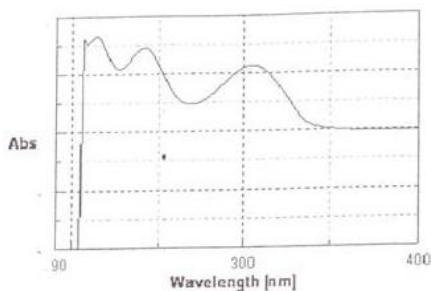
Parameters	Capecitabine	Guar gum	Xanthan gum
Bulk density(g/ml)	0.38	0.75	0.68
Tapped density(g/ml)	0.45	0.88	0.79
Carr's compressibility Index(%)	15.55	14.33	13.92
Haussener's ratio	1.18	1.17	1.16
Angle of repose(*)	39.09	31.06	33.16

*All values represent mean \pm SD (n = 3).

Table 1: Flowability of drug and polymers*

In the present study, Capecitabine was characterized by thermal (DSC), crystallographic (X-RPD), microscopic (SEM) and spectroscopic (FT-IR). Drug excipient interactions studied by spectroscopic (FT-IR) evaluation. Influence of morphology of drug as well as polymers on flow behavior was also investigated. Capecitabine was also studied for pH dependent solubility and accelerated stability studies.

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**Fig. 1. UV spectrum of Capecitabine**

2. MATERIALS AND METHODS

Capecitabine, Guar Gum and Xanthan Gum were obtained as a gift sample from Cipla Pvt. Ltd., Mumbai. Chitosan obtained from Central Institute of Fisheries and Technology, Cochin, Eudragit® FS 30D obtained as a gift sample from Lupin Ltd, Pune. All other chemicals and reagents used were of "Analytical Grades".

Determination of λ_{max} :^[11]

A solution 0.1 % w/v of capecitabine was prepared. Accurately weighed 100 mg of drug and were dissolved in 100ml methanol. A solution was kept in fused silica cell and UV spectrum was recorded by using Jasco – 4100 UV spectrophotometer in the wavelength range 200- 800 nm.

Infrared spectroscopy:^[11,12,13]

Fourier - transform infrared (FT-IR) (Make- Jasco 4100 FT-IR) spectra of capecitabine was obtained over the wave number range of 4000 to 400 cm⁻¹.

Surface Topography:^[13,14]

The surface topography of pure drug was analyzed with a scanning electron microscope operated at an accelerated voltage of 10 kv and at magnifications 350, 500, 1000 and 2000 respectively.

Flowability:

Angle of repose was determined by fixed funnel method^[15,16]. Accurately weighed powder blend was poured in the glass funnel. The height of funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of powder. The powders were allowed to flow through a glass funnel freely onto a clean surface. The diameter of the powder cone so formed was measured and angle of repose was calculated using the following equation:

$$\tan \theta = h/r, \text{ Therefore; } \theta = \tan^{-1} (h / r)$$

Where, h is the height of powder cone and r is the radius of the powder cone.

Tapping cylinder method was used for determining bulk density (ρ_b) and tapped density (ρ_t) using Bulk Density Apparatus^[17]. Powder was taken in a 50 ml measuring cylinder and the initial volume (bulk volume) and the volumes after 50 tapping were measured.

Bulk density (ρ_b) and tapped density (ρ_t) were calculated using the following formulae:

$$\rho_b = \text{Weight of the powder (W)} / \text{Volume of the packing (V}_b\text{)}$$

$$\rho_t = \text{Weight of the powder (W)} / \text{Tapped volume of the packing (V}_t\text{)}$$

Carr's Compressibility Index and Haussner's ratio were calculated from the following equations.

$$\text{Carr's compressibility index (\%)} = [(\rho_t - \rho_b) / \rho_t] \times 100$$

$$\text{Haussner's Ratio} = \rho_t / \rho_b$$

X-ray powder diffraction:^[11,18]

The X – RPD patterns was recorded by using Philips PW 1729 X- ray diffractometer. Sample analyzed up to 50° 2θ. The voltage and current used were 30kv and Ma, respectively.

Differential scanning calorimetry (DSC):^[18]

DSC thermogram was obtained by using, Model-9900 (DUPONT, USA). The sample was exposed to heating rate of 10 °C / min over a temperature range of 10 – 400 °C under nitrogen purging.

Saturation solubility study:^[13,19,20]

At room temperature (25 to 27 °C), saturated solutions were prepared by dissolving excess amounts of capecitabine in to water and buffer solutions with pH ranging from 1.2 to 8.0. The pH of the solution was adjusted by hydrochloric acid and sodium hydroxide. A suspension was shaken by Griffin Flask Shaker (Wrist Action Shaking Machine). Small volumes of these solutions were filtered and diluted as necessary and absorbance determined spectrophotometrically.

Drug-Excipient interaction study:^[13,21,22]

Drug – excipients mixture of 1:1 ratio accurately weighed and compatibility of freshly prepared mixtures was determined by FTIR spectroscopy.

Accelerated stability study:^[20,23,24]

To assess the solid - state stability, studies were done at 40°C/ 75% RH for three months. Analysis was carried out by FT-IR (Make - Jasco 4100 FT-IR) and observed organoleptic properties.

3. RESULTS AND DISCUSSION

The wavelength of maximum absorbance (λ_{max}) was found to be 240 nm for capecitabine (Fig. 1). IR spectrums of capecitabine (Fig. 2) indicated characteristic peaks belonging to major functional groups. However, bands appearing at 3432 and 3234 cm⁻¹ are due to O–H/N–H stretching vibrations. The band at 1684 cm⁻¹ is due to pyrimidine carbonyl stretching vibrations, whereas bands at 1721 and 1756 cm⁻¹ are due to urethane carbonyl stretching vibrations. Characteristic band at 1042 indicate C–F stretching vibrations.

Scanning electron microphotographs of the capecitabine showed (Fig. 3) irregular shape having cracks on surface with pores and has rough surface. Values for angle of

repose indicated good flow properties of drug and polymers and this was further supported by lower Carr's compressibility index values and Haussner's ratio (Table 1). X-RPD patterns (Fig. 4) of capecitabine investigate the crystallinity of capecitabine, has shown characteristic intense peaks at 2θ of 5° , 20° and 25° . DSC thermograms (Fig. 5) of capecitabine showed two endothermic peaks, one broad and asymmetric at 125°C , which corresponds to melting process and the other at 159°C due to thermal decomposition. All thermal data also supported crystalline nature of Capecitabine.

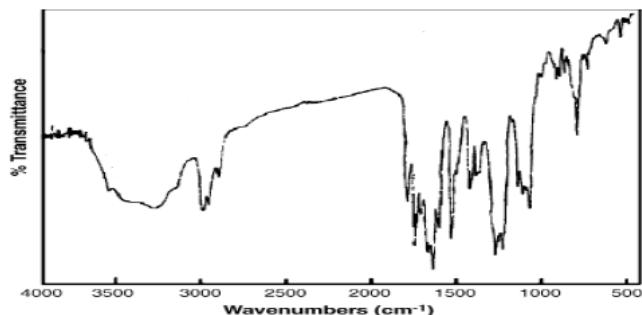


Fig. 2. FT-IR spectra of Capecitabine

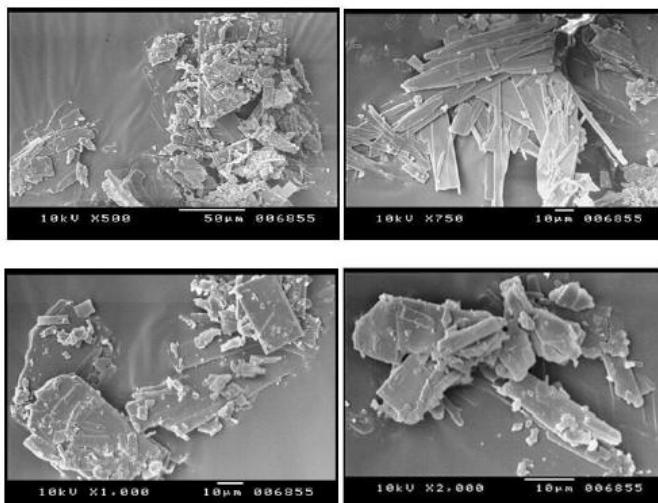


Fig. 3. SE Microphotographs of Capecitabine

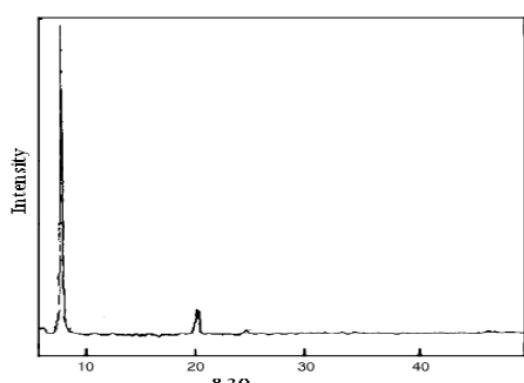


Fig. 4. X-RPD patterns of Capecitabine

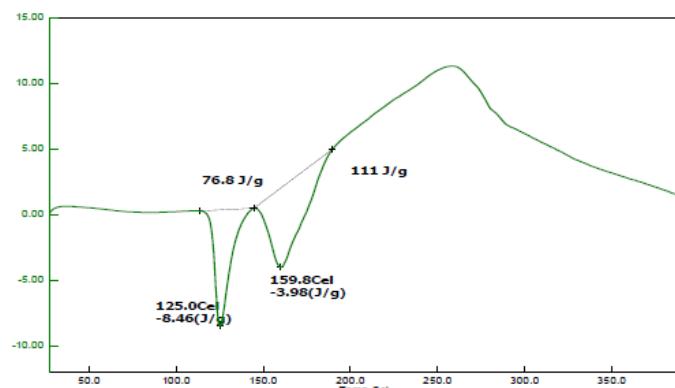
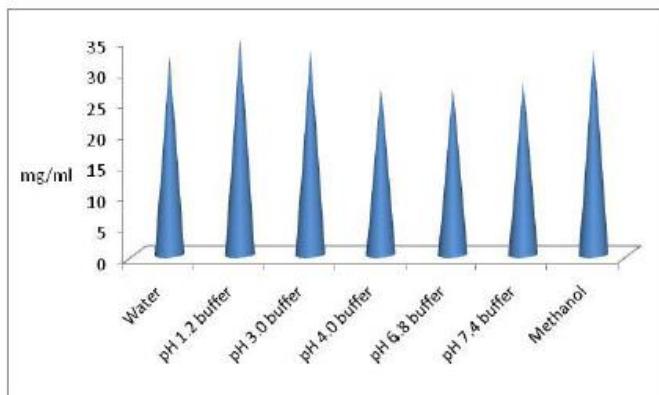
Fig. 5. DSC thermograms of Capecitabine at a heating Rate of $10\text{ }^{\circ}\text{c}/\text{min}$ 

Fig. 6. Solubility profile of capecitabine

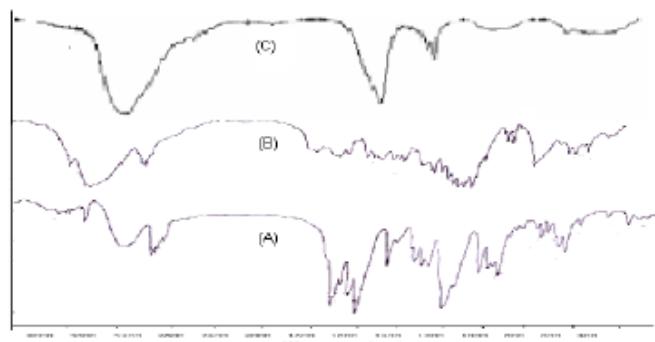


Fig. 7. Drug-Excipient interaction study: FTIR Spectras of plain drug, Capecitabine (A), Capecitabine + Eudragit FS 30D (B) and Capecitabine + Chitosan (C)

The pH saturation solubility study for Capecitabine was showed significantly high solubility in water, methanol and acidic buffer, also showed good solubility in all pH buffers (Fig. 6). The compatibility of drug and excipients at accelerated conditions checked out by infrared (IR) profile of physical mixtures, which were compared with IR spectrum of drug and excipients (fig. 7 & 8). It was observed from the spectra obtained that characteristic peaks appears with identical or with minor differences, at frequencies, 1718.47 cm^{-1} is due to pyrimidine carbonyl stretching; 1040 cm^{-1} indicating C-F stretching vibrations for Capecitabine. However no significant changes in characteristic peaks associated with specific structural characteristic of the drug molecule was observed,

indicating absence of interaction between the drug and the polymer. IR spectra of pure drug after stability study did not show any significant changes in the characteristic peaks of Capecitabine, thus indicating good stability of drug at accelerated conditions. Also no changes were observed in organoleptic properties after stability studies.

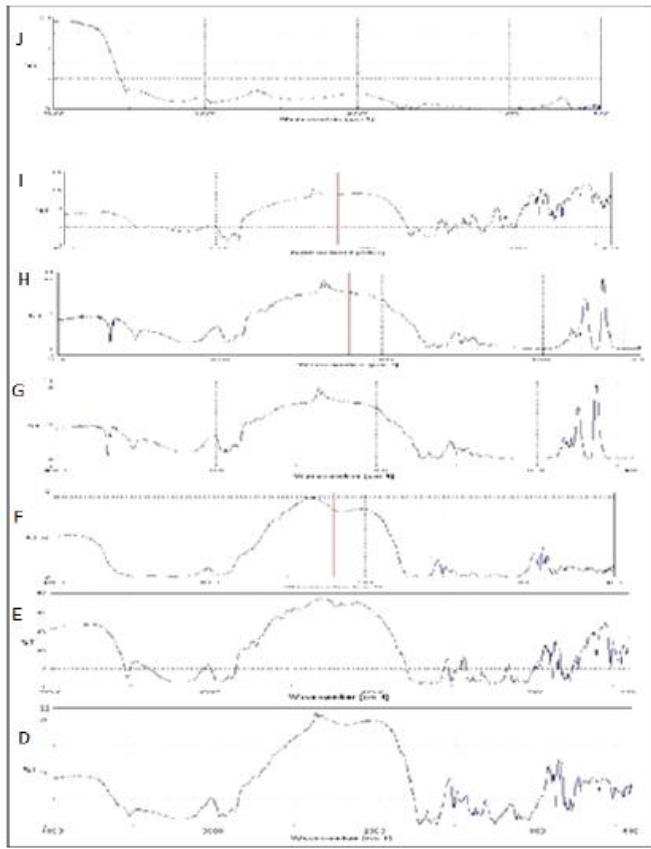


Fig. 8. Drug-Excipient interaction study: FTIR Spectras guar gum & drug (D), dicalcium phosphate & drug (E), talc & drug (F), eudragit I100 (G), drug & lactose (H), xanthan gum (I) and guar gum (J)

4. CONCLUSION:

A well designed characterization study of drug and polymers provides a sound base on which to build a rapid and economical formulation development program. Hence, from the above studies it can be concluded drug and polymers showed good micromeritic properties. Drug showed nearly same response for solubility at overall pH range and good stability at accelerated conditions. Results shown the feasibility of using polymers like, guar gum, xanthan gum, chitosan, eudragit FS 30 D and other excipients for formulating sustained-release matrix tablets or multiparticulate colon targeting dosage forms of capecitabine.

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