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SHORT COMMUNICATION

# Designing and evaluation of extended release matrix tablet containing altretamine–HP-β-CD inclusion complex

**Bina Gidwani**[1] · **Amber Vyas**[1]

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**Abstract** The aim of present study was to prepare sustained release tablets of a poorly soluble anticancer drug using cyclodextrin complexation as a potential approach. Altretamine is an alkylating agent practically insoluble in water and posses poor oral bioavailability. For this, the most suitable binary system of ALT-HP-β-CD was selected to improve the aqueous solubility and then embedding the complexed drug into a matrix tablet with fusion method. Tablets were prepared using glycerol monostearate (GMS) and polyethylene glycol 4000 (PEG4000). Complexes were prepared at different ratios and mixed with other excipients to achieve tablets with efficient dissolution profile complying with the requirements for sustained delivery of solid dosage forms. Results of Fourier Infrared spectroscopy (FTIR), differential scanning calorimetry (DSC) and X-ray diffractometry (XRD) proved that kneading was most efficient technique for preparation of amorphous cyclodextrin inclusion complex with ALT and entrapping this complex into tablet. Dissolution profile of ALT was enhanced significantly in pH 6.8 from the binary system and significant within the limits ($t$ test Student $p < 0.05$). The release kinetics of the tablets showed that diffusion was responsible for controlling the release from the tablets.

**Keywords** Altretamine · Cyclodextrin · Matrix tablet · Sustained release

✉ Amber Vyas
ambervyas@gmail.com

Bina Gidwani
beenagidwani@gmail.com

[1] University Institute of Pharmacy, Pt. Ravishankar Shukla University, Raipur, Chhattisgarh, India

## Introduction

Drug release is a rate limiting step for oral drug bioavailability, mainly for drugs with low gastrointestinal solubility and high permeability [1]. Poorly soluble drugs are associated with slow drug absorption leading to inadequate and variable bioavailability [2]. Also, the therapeutic efficiency of a drug depends basically on the ability of the dosage forms to deliver the active ingredient to its site of action at a rate and amount sufficient to elicit the desired pharmacological response [3].

Altretamine is an alkylating antineoplastic agents used in treatment of ovarian cancer. Its poor solubility and low bioavailability hinders its clinical efficacy. It is a highly lipid-soluble drug [4, 5]. The common name of altretamine is hexamethylmelamine (HMM). Chemically it is N, N, N′, N′, N″, N″-hexamethyl-1,3,5-triazine-2,4,6-triamine. Thus, it is important to enhance the solubility and dissolution rate of altretamine to improve its oral bioavailability. The structure of altretamine is shown in Fig. 1.

Cyclodextrins are family of water soluble, macrocyclic compounds capable of forming inclusion complexes and alleviating the undesirable properties of drugs [6]. Cyclodextrins also provide sustained/controlled/delayed release properties to certain active compounds. Hydroxypropyl-β-cyclodextrin (HP-β-CD) is widely used to solubilize and stabilize various compounds of BCS (Biopharmaceutical Classification System) class II and class IV. HP-β-CD is most employed for complexation due to its lower toxicity compared to parent CDs. It is the first approved derivative of cyclodextrin by FDA with higher water-solubility and better biocompatibility [7, 8].

In the present study, an attempt was made to improve the solubility and dissolution rate of altretamine by complexing with HP-β-CD thereby increasing its bioavailability and

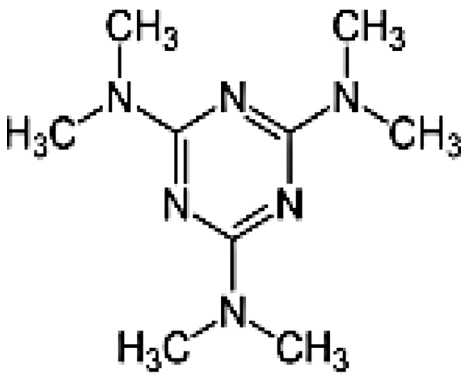

**Fig. 1** Structure of altretamine

therapeutic efficacy. The prepared complexes (binary systems) were characterized by differential scanning calorimetry (DSC), FTIR (Fourier Transform Infrared Spectroscopy), drug content and X-ray diffractometry (XRD). Complexes were prepared by kneading and co-evaporation method in 1:1 M ratio. The best complex was then formulated into matrix tablet using GMS as inert substance and PEG 4000 as channeling agent to achieve sustained release of altretamine.

## Materials and methods

Altretamine (ALT) was purchased from Akshaya Lab. Pvt. Ltd. Hyderabad, India. Hydroxy-Propyl-β-Cyclodextrin (HP-β-CD) (Degree of substitution 4.2) was provided as gift sample from Roquette, France. Glycerol monostearate (GMS), lactose and talc were purchased from Merck (Germany). Polyethylene glycol (PEG4000) was purchased from Inter Pharm Ltd. (UK). Lactose was purchased from Himedia. All other reagents and chemicals used in the study were of analytical grade.

## Experimental work

### Preparation of binary inclusion system

The binary inclusion complexes of ALT with HP-β-CD were prepared by kneading and co-evaporation method.

*Kneading method*

Kneaded complex between ALT and HP-β-CD were prepared in 1:1 M ratio by accurately weighing 210 and 1592 mg respectively and were then mixed and kneaded in a mortar using water: ethyl alcohol (1:1 v/v) as the solvent system for 45 min. This remaining solvent in the mixture was evaporated in an oven at 40 °C for 48 h. Finally the powdered complex was collected and milled in a mortar [9].

*Co-evaporation method*

Inclusion complex of ALT with HP-β-CD was prepared in a 1:1 M ratio by the co-evaporation method using ethyl alcohol the solvent. For this, ALT and HP-β-CD were weighed equivalent to 210 and 1592 mg respectively and dissolved separately in ethanol and then mixed for 60 min. The solvent remaining in the mixture was evaporated with a rota-evaporater (BUCHI R-200, Switzerland) at 65 °C at 100 rpm. The resultant complex was collected and stored over silica in a desiccator at room temperature [10]. These complexes are prepared on the basis of their molecular weight (altretamine and HP-β-CD) in 1:1 M ratio.

*Preparation of physical mixture*

The physical mixtures of ALT with excipients (ALT: GMS) and (ALT: HP-β-CD): GMS were prepared by simply mixing the accurately weighed equimolar amount of the wax GSM, drug ALT and cyclodextrin (HP-β-CD).

### Preparation of solid dispersion

Solid dispersions were prepared by fusion method. Accurately weighed GSM and PEG 4000 were placed in a porcelain dish and melted in a thermostatically-maintained water bath at 75 °C. When this mixture was melted homogenously, then the accurately weighed amount of drug ALT or the binary system of ALT: HP-β-CD was added and mixed properly with uniform stirring. The molten mass obtained was solidified by cooling over ice. The amount of drug, excipients and inclusion complex used for solid dispersion is shown in Table 1. The resulting solid dispersion was stored in desiccators over silica for 48 h. The obtained particles were passed through sieve of different sizes (314 and 100 μm) (CISA SIEVE SHAKER, MOD.RP.09, SPAIN) prior to their dissolution studies [11].

### Characterization of binary inclusion systems

The prepared inclusion complexes were characterized by FTIR, DSC and XRD studies.

*FTIR studies*

The FTIR spectra of pure drug ALT, hydroxy propyl-β-cyclodextrin (HP-β-CD), glycerol monostearate (GMS) and their mixtures were obtained by FTIR spectroscopy

**Table 1** The composition of altretamine systems

| Altretamine systems | Altretamine (mg) | HP-β-CD (mg) | GMS (mg) | PEG 4000 (mg) |
|---|---|---|---|---|
| Kneaded complex (ALT: HP-β-CD) (1:1 M) [S1] | 20 | 132.6 | – | – |
| Co-evaporated complex (ALT: HP-β-CD) (1:1 M) [S2] | 20 | 132.6 | – | – |
| Solid dispersion ALT: GMS (1:5 w/w) [SD1] | 20 | – | 102 | – |
| Solid dispersion ALT: GMS : PEG 4000 (1:5:2.5 w/w) [SD2] | 20 | – | 102 | 53 |
| S1:GMS [S3] (1:1) w/w | 20 | 132.6 | 102 | – |
| S1:GMS:PEG 4000 [S4] (1:1:0.5) (w/w/w) | 20 | 132.6 | 102 | 53 |

(FTIR spectroscopy, Shimadzu 8400 S, Japan). The samples (approx. 1 % w/w) were mixed with KBr powder and compressed to a 12 mm disc by a hydraulic press at 10 tons compression force for 30 s. The disc was placed in the sample holder and scanned from 400 to 4000 $cm^{-1}$ and the scans were recorded.

*DSC*

Differential scanning calorimetry (DSC) thermograms of the samples were recorded using a thermal analysis system (SETARAM.DSC 131, France). After calibration with indium and lead standards, the samples were heated at 10 °C/min in an aluminum pan under nitrogen atmosphere. A similar empty pan was used as the reference. The samples were scanned from 25 to 300 °C.

*XRD*

The X-ray diffractograms of the powdered samples were collected using diffractometer (STOE, Germany).The instrument used monochromated CuKa radiation at k = 1.5406 Å. All the samples were analyzed through a 2 h range of 5–30° with the scanning speed 0.05 step.

## Preparation of matrix tablet

Tablets were prepared by mixing powder of pure drug or the binary inclusion systems with avicel PH101 and lactose in a mortar for 15 min. Talc was added to this and mixed uniformly for about 5 min. This mixture was then compressed into tablets by direct compression using a single punch tableting machine (Erweka AR 402, Germany) with a flat-faced punch (8 mm diameter). The composition of tablets is presented in Table 2.

**Table 2** Composition of matrix tablets of altretamine systems

| Formula (mg) | F1 | F2 | F3 | F4 | F5 | F6 |
|---|---|---|---|---|---|---|
| Altretamine | 20 | 20 | 20 | 20 | 20 | 20 |
| Avicel PH 101 | 65 | 65 | 65 | 65 | 65 | 65 |
| Lactose | 355 | 223 | 150 | 227 | 95 | 25 |
| Talc | 10 | 10 | 10 | 10 | 10 | 10 |
| SD1 | – | 152 | – | – | – | – |
| SD2 | – | – | 225 | – | – | – |
| S1 | – | – | – | 148 | – | – |
| S3 | – | – | – | – | 280 | – |
| S4 | – | – | – | – | – | 350 |

## In vitro evaluation of binary system and tablets

*Evaluation of matrix tablet*

The prepared tablets were evaluated for Hardness, friability, thickness and weight variation.

Hardness of the tablets was determined using a hardness testing apparatus (Pfizer).

Friability of the tablets was measured using Roche friabilator. Tablets of a known weight ($W_0$) were de-dusted in a drum for a fixed time (approx. 100 revolutions) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1 % w/w.

$$\%\,\text{Friability} = (W_0 - W)/W_0 \times 100$$

*Drug content*

For estimation of drug content, an accurately weighed 100 mg of ALT was dissolved in 10 ml methanol in a volumetric flask to prepare 10 mg/ml solution. The sample was

measured by UV spectrophotometer (Shimadzu 1700, Japan) at 227 nm and the concentration of ALT was calculated from the standard curve prepared simultaneously [12].

*Dissolution studies*

An accurately weighed amount of the binary inclusion complex containing ALT equivalent to 20 mg was placed in each vessel in a modified USP dissolution basket covered with the stainless steel screen (mesh size 100 lm) (Pharmatest PTDT7, Germany). Dissolution study was carried out in 900 ml dissolution medium (0.1 N HCl, pH 1.2, Sorenson buffer pH 6.8). The basket was rotated at 100 ± 5 rev/min, and the dissolution medium maintained at 37 °C. Aliquot of the samples were withdrawn with replacement at 5, 10, 15, 30, 45, 60, 90 and 120 min. These samples were filtered by using 0.45 µm, Millipore and properly diluted, their absorbance was measured at 227 nm [13]. The corresponding concentrations were determined from the linear regression equation of the standard curve run simultaneously. The dissolution study was carried out at room temperature 37 ± 0.5 °C which clarifies that the drug altretamine undergoes no degradation. The temperature was controlled using thermostat.

Similarly, the dissolution study of the prepared tablets was carried out using USP dissolution apparatus II. The dissolution medium used was 900 ml 0.1 N HCl for 2 h and then changed to Sorenson buffer pH 6.8 for addition 6 h. All the other conditions (temperature and rotation speed) were the same as for the pure drug ALT and the binary inclusion complex.

Furthermore, the data obtained from in-vitro drug release study were analyzed by different kinetic models (Korsmeyer and Peppas model and Peppas and Sahlin equation) in order to determine the exact release mechanism of drug from the matrices.

### Statistical analysis

All the data were statistically analyzed by student's *t*-test using SPSS statistical software (SPSS Version 13). Results were reported significant with $p < 0.05$.

## Results

### Preparation of inclusion complexes

Phase solubility study of ALT with HP-β-CD revealed $A_L$ type solubility curve, which indicated linear increase in solubility of ALT with increase in concentration of HP-β-CD. Inclusion complexes (binary systems) were prepared by kneading and co-evaporation method in 1:1 M ratios.

### DSC

DSC is important tool to estimate the qualitative information about physicochemical properties of drug in complex. Also, it is used to determine the effect of additives on the thermal behavior of materials. The DSC thermograms of the complexes and samples are shown in Fig. 2. The thermogram of pure drug altretamine showed a sharp endothermic peak at 172 °C corresponding to its melting point, confirming the crystalline nature. In case of the kneaded complex of ALT: HP-β-CD the peak of Alt was disappeared indicating that the drug is inclused within the complex whereas the characteristics peak of ALT was shifted towards lower temperature (145.2 °C) in the co-evaporated complex. This suggests that true complexation existed in kneaded system and partial or incomplete complexation occurred in co-evaporated binary systems with the formation of an amorphous solid dispersion. This may account to better dissolution profile with sustained release of ALT. However, the thermogram of solid dispersion (ALT: GMS) showed the characteristics melting peak at 170 °C along with the slight shift in the peak of GMS from 67 to 64 °C. This indicates that the drug ALT has not undergone any significant change during preparation of the solid dispersion. Meanwhile, the thermograms of physical mixture were similar to that of peaks obtained with pure samples; this was evidence that very little or no complexation existed in physical mixtures of the samples [14].

### X-ray diffraction (XRD)

The diffraction patterns of all the samples i.e. pure ALT, HP-β-CD, GMS, binary inclusion complexes prepared by kneading, co-evaporation and physical mixtures and solid dispersions are shown in Fig. 3. Pure ALT exhibited characteristic peaks at 14°, 21°, and 32° confirming the crystalline nature of drug [15]. Although, no specific characteristic peak appeared on the X-ray diffractometer of HP-β-CD revealing that it existed in amorphous nature. Similarly, the diffraction pattern of kneaded and co-evaporated inclusion complex were diffraction from that of the single components, they showed diffused and shifted diffraction pattern. It revealed that ALT was truly and wholly entrapped within the complex. Disappearance of crystallinity and the changes seen in the binary system indicated a strong interaction in kneaded complex contributing to improved dissolution behavior of ALT in the intestinal media.

### FTIR spectroscopy

FTIR spectroscopy was used to assess the interaction between the host and the guest molecules in the solid state.

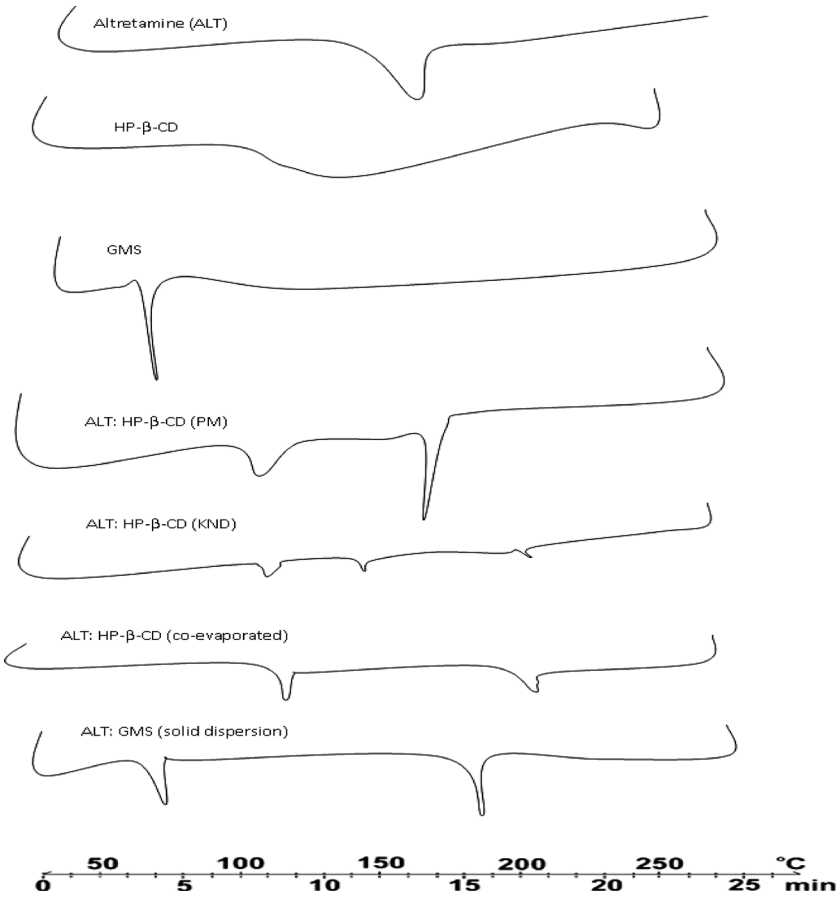


**Fig. 2** DSC thermograms of pure ALT, HP-β-CD, GMS, Inclusion complexes prepared by physical mixture, kneading and co-evaporation method, solid dispersion

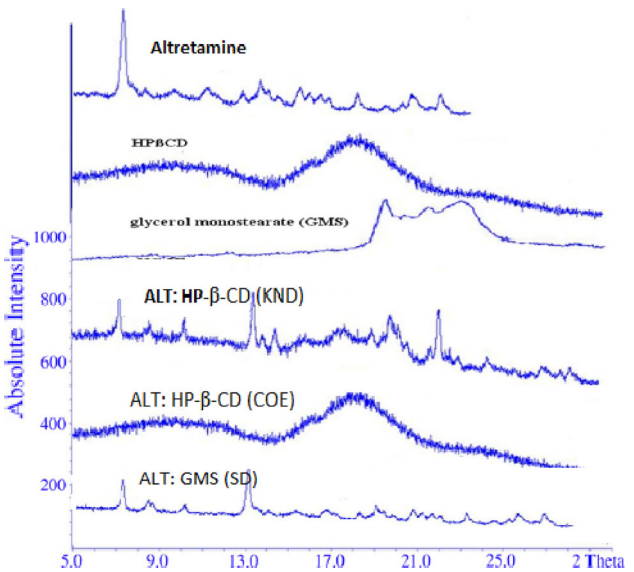


**Fig. 3** X-ray diffractogram of Pure ALT, HP-β-CD, GMS, Inclusion complexes prepared by kneading and co-evaporation method, solid dispersion

Disappearance of peaks, slight shifts or changes in the absorption spectrum indicates formation of true inclusion complex [16]. The FTIR spectra of HP-β-CD showed prominent peaks at 3416 $cm^{-1}$ (for O–H stretching vibrations), 2930 $cm^{-1}$ (for C–H stretching vibrations), and at 1169, 1076 $cm^{-1}$ (for C–H, C–O stretching vibration). The FTIR spectra of ALT showed characteristic peaks and bands at 1675 $cm^{-1}$ (for C–O stretching), 1390, 1054 $cm^{-1}$ (for O–H stretching, C–O–C stretching), 3420.60 $cm^{-1}$ (N–H stretch), 2927 $cm^{-1}$ (–CH stretching), 1540.25 $cm^{-1}$ (–C=N stretching), 1505.2 $cm^{-1}$ (N–CH3 stretching), 1213. 65 $cm^{-1}$ (C–N stretching), 1051 $cm^{-1}$ (C–H bending). In kneaded complex, the absorption band of ALT shifted towards a higher wavelength of 1970 $cm^{-1}$ confirming the existence of true interaction between ALT and HP-β-CD. Also, the decrease in the intensity of C‘O stretching band was maximum for kneaded complex and minimum for physical mixture. In physical mixture, all the peaks of ALT were clearly visible with no significant changes.

Thus, the solid state studies carried out by DSC, X-ray diffraction and FT-IR resulted that the kneaded complex was effective in preparing amorphous cyclodextrin complexes with ALT which may led to increase in dissolution rate of ALT in intestinal media. Figure 4 shows FTIR spectra of pure ALT, HP-β-CD, GSM and ALT: GMS solid dispersions.

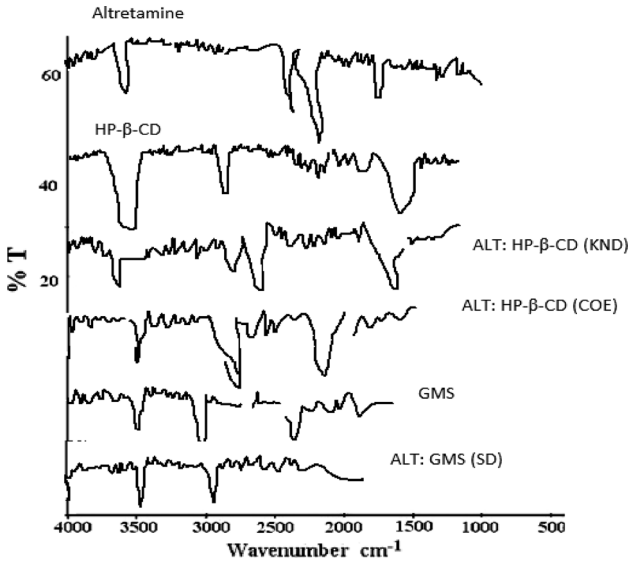


**Fig. 4** FTIR spectra of ALT, HP-β-CD, GMS, Inclusion complexes prepared by kneading and co-evaporated method, solid dispersion

## Evaluation of tablets

Data of hardness of tablet formulations, their thickness and friability is shown in Table 5.

All the prepared matrix tablets (F1–F6) have hardness in the range from 4.9 to 6.3 kg/cm$^2$ and thickness in the range from 4.0 to 4.5 mm with percentage friability in the range from 0.01 to 0.025 %.

## Drug content in binary systems

The percentage of actual drug content in each system of ALT was determined. The results are shown in Table 3. All the systems showed a good agreement between theoretical and actual drug contents. The drug content ranged from 96 to 100 %.

**Table 3** Drug content in the altretamine system

| Altretamine system | % Drug content (±SD) |
|---|---|
| Kneaded complex (ALT: HP-β-CD) (1:1 M) [S1] | 99.74 ± 0.43 |
| Co-evaporated complex (ALT: HP-β-CD) (1:1 M) [S2] | 96.12 ± 0.86 |
| Solid dispersion ALT: GMS (1:5 w/w) [SD1] | 99.86 ± 0.14 |
| Solid dispersion ALT: GMS : PEG 4000 (1:5:2.5 w/w) [SD2] | 98.71 ± 0.38 |
| S1:GMS [S3] (1:1) w/w | 98.64 ± 0.11 |
| S1:GMS:PEG 4000 [S4] (1:1:0.5) (w/w/w) | 100.02 ± 0.17 |

## In-vitro dissolution studies

As altretamine is practically insoluble in water, the dissolution profiles of pure ALT in 0.1 N HCl, pH 1.2, shows that 60.17 ± 0.52 % of ALT was dissolved after 2 h as compared to the dissolution study in Sorenson's buffer, pH 6.8, where only 25.26 ± 0.86 % of ALT was dissolved after 2 h. Figure 5 shows the dissolution profile of ALT at pH 1.2 and pH 6.8

In case of inclusion complexes, the dissolution of 1:1 M ratio ALT: HP-β-CD kneaded complex was compared with that of co-evaporated system in buffer pH 6.8. The dissolution profiles are shown in Fig. 6. It was found that dissolution rates of kneaded products were significantly higher as compared to co-evaporated system. The results of kneaded complex were significant as confirmed by students t-test ($P < 0.05$). This may be due to the entrapment of ALT within the cavity of HP-β-CD and formation of amorphous solid dispersion as confirmed by DSC and XRD. Altretamine is a BCS class II drug which undergoes chemical degradation under acidic pH, basic pH, elevated thermal conditions and in oxidative environment. During formulation of matrix tablet; drug complexed with cyclodextrin (HP-β-CD) was used which protects the drug form all degradation conditions. As cyclodextrins are known to protect the drug substance from degradation and impart chemical stability to the drugs.

## Release of altretamine from the tablets

In total 6 formulations were prepared. In formulation F1 which contained pure ALT alone, the percentage of drug dissolved was 21.19 ± 0.21 % after 2 h in the acidic condition (pH 1.2). In formulation F2 containing ALT: GMS [SD1], the percent of ALT dissolved was

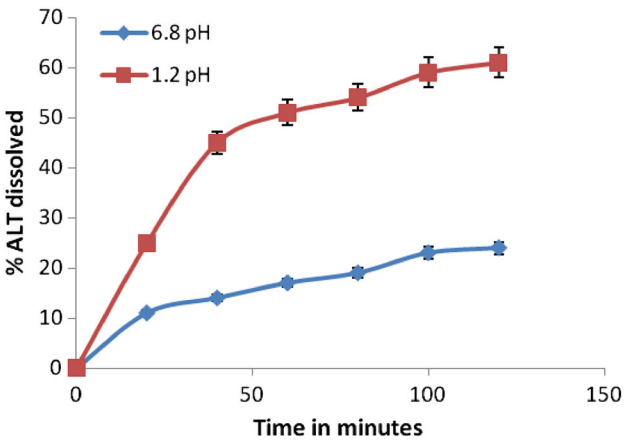


**Fig. 5** Percentage of altretamine dissolved in 0.1 N HCl pH 1.2 and Phosphate buffer pH 6.8

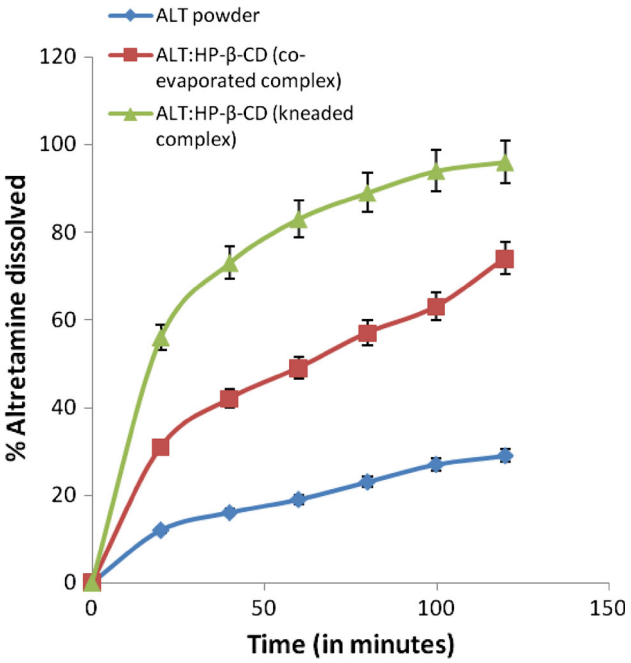


**Fig. 6** Percent of altretamine dissolved in pure drug suspension, kneaded and co-evaporated complex (in 0.1 N HCl pH 1.2 for 2 h and in Phosphate buffer pH 6.8 for next 6 h)

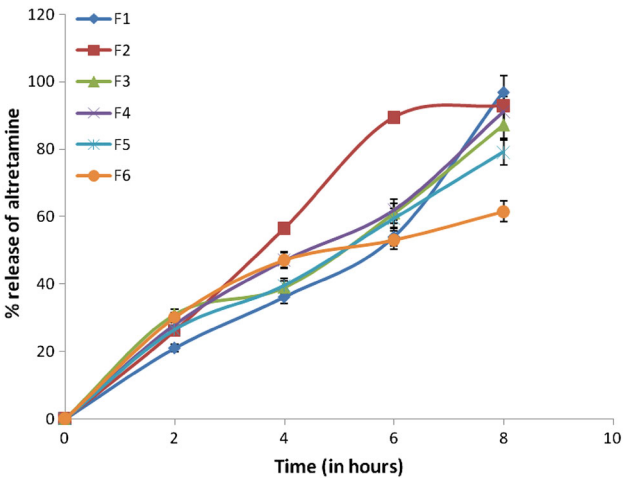


**Fig. 7** Percent release of altretamine from all the tablet formulations [F1–F6]

26.15 ± 1.097 after 2 h. In formulation F3 containing PEG 4000 with SD 1; the percent of ALT dissolved was increased to 87.19 ± 1.02 % after 8 h. This improvement in percent release was due to a channel created inside the tablet and as a result of this the percent of ALT released was elevated. Furthermore, by decreasing the amount of GMS in formulation F4, the percent of ALT dissolved was 91.17 ± 1.13 % after 8 h. There was no significant change in percent of ALT dissolved after 2 h in formulations F2-F4 due to change in dissolution medium from 0.1 N HCl pH 1.2 for 2 h to phosphate buffer pH 6.8 for 6 h. The percent of ALT released from formulation F5 which contained kneaded inclusion complex was 79.53 ± 1.9 after 8 h. This is evidence that method of complexation (kneading) led to controlled release of tablet. This may be due to the entrapment of drug within the cavity of HP-β-CD along with the formation of amorphous solid dispersion. The drug release from formulation F6 was 30.12 ± 1.3 % after 2 h in acidic medium (pH 1.2) and 47.16 ± 1.43 % at 4 h and 61.58 ± 1.22 % at 8 h in phosphate buffer (pH 6.8). The results show that the formulation F6 showed significantly higher rates of dissolution under all conditions. Figure 7 shows the release of altretamine from formulations F1–F6.

Furthermore, the results of the dissolution profiles of ALT from tablets containing pure ALT and from the matrix system (GMS: PEG4000) in combination with the kneaded binary inclusion system were fitted in unpaired Student *t* test, $p < 0.05$. The dissolution profile of formulation F6 was in agreement with the dissolution requirements specified by the USP. Thus, the presence of glycerol monostearate (GMS) with PEG4000 provided an extended release of ALT in the presence of HP-β-CD. Formulation F6 showed sustained release of altretamine from the matrix tablet which is due to use of unique combination of HP-β-CD with GMS and other excipients. Cyclodextrin led to increase in solubility and GMS led to sustained release effect. Enhancement of solubility of altretamine through cyclodextrin complexation led to improved dissolution. For all the prepared formulations, the mass balance was achieved with maximum utilization of drug. Mass balance is also known as AME (absorption, metabolism and excretion) studies. These studies are used to estimate the recovery of drug after dissolution. Mass balance is a term that refers to balancing the amount of drug administered as a dose to the amount of drug-related material collected in human excreta. Acceptable values for recovery, such as 85–90 % have been proposed. In present work, after the dissolution study mass balance was achieved in all the formulations (F1–F6) with recovery of more than 75 % in each formulation.

**Table 4** Drug release kinetics

| Formula | N | Kp | $R^2$ |
|---|---|---|---|
| F2 | 0.381 | 0.416 | 0.914 |
| F3 | 0.316 | 0.571 | 0.931 |
| F4 | 0.340 | 0.522 | 0.956 |
| F5 | 0.372 | 0.541 | 0.973 |
| F6 | 0.741 | 0.692 | 0.997 |

**Table 5** Evaluation parameters of prepared tablet formulations

| Parameters | F1 | F2 | F3 | F4 | F5 | F6 |
|---|---|---|---|---|---|---|
| Tablet Hardness (kg/cm$^2$) | 5.1 ± 0.06 | 5.8 ± 0.14 | 5.6 ± 0.22 | 6.1 ± 0.17 | 5.2 ± 0.12 | 4.9 ± 0.73 |
| Thickness (mm) | 4.5 ± 0.01 | 4.2 ± 0.08 | 4.9 ± 0.03 | 4.7 ± 0.02 | 4.4 ± 0.01 | 4.6 ± 0.21 |
| Friability (%) | 0.022 | 0.005 | 0.0124 | 0.019 | 0.013 | 0.004 |

### Kinetics of the release of ALT from the tablets

Applying the datas of dissolution studies in Korsmeyer and Peppas model [17] the values of n for F2–F4 and F5 were less than 0.45 which indicated that the release mechanism followed Fickian diffusion [18]. The higher dissolution rate and extent of drug released in the first two hours (in acidic condition) was due to greater extraction of drug from the vicinity of the matrix surface. ALT is highly soluble in acidic pH so, is released immediately when it came in contact with the dissolution media. The drug release was controlled by presence of GMS, which show negligible swelling property and the matrix prepared posses hydrophobicity. Moreover the use of lactose and avicel also contributed in drug release [19]. In formulation F6, the value of n was 0.74, which indicates the release mechanism followed anomalous behavior or non-Fickian transport. This may be due to swelling and dissolution of matrix of tablet causing deviation from the Fickian release. The use of PEG4000 in tablet formulations led to enhancement in the penetration of dissolution medium into the matrix; thereby facilitating creation of more pores inside the tablet, due to which drug was dissolved rapidly [20]. Table 4 highlights the data of release kinetics of altretamine from matrix tablets.

## Conclusion

The results of present work showed that kneading method was most efficient over co-evaporation method in improving the aqueous solubility of ALT. Meanwhile the matrix tablet prepared with GMS and PEG4000 was efficient in controlling the release of ALT during 8 h. Diffusion was the predominant mechanism for drug release from all the prepared matrix tablets. Results of FTIR, DSC and XRD confirmed the formation of amorphous solid dispersion indicating inclusion of ALT within the cavity of HP-β-CD cavity. In future, in vivo studies and estimation of pharmacokinetic parameters will be useful for improving therapeutic efficiency of altretamine and oral delivery system. The release of Altretamine from the matrix tablet F6 formulation was slow and sustained which is due to the use of cyclodextrins and GMS in the matrix tablet.

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**Compliance with ethical standards**

**Conflict of Interest** None.

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