https://ijrps.com

ISSN: 0975-7538
Research Article

Formulation and evaluation of fast disintegrating tablet containing capecitabine for dysphagia patients

Dixit Anil S *and Kulkarni PK

Department of Pharmaceutics, JSS College of Pharmacy, JSS University, Mysore, 570015, Karnataka, India

ABSTRACT

Capecitabine (CAP), an anticancer agent used for breast and colorectal cancer has high and variable dosage regimen based on body surface area. Due to high dose, around 3 to 7 tablets are swallowed each time. Dysphagic patients experience difficulty in swallowing the conventional tablets and consequently do not take medications as prescribed. Hence the aim of the present research was to overcome the swallowing problem by developing fast disintegrating tablet (FDT) which disintegrates rapidly when placed on the tongue. FDT was prepared and optimized by wet granulation technique incorporating various superdisintegrants and other excipients. The granules prepared showed good flow and compressible property; hence tablets produced were of uniform weight with acceptable weight variation. Drug-excipient compatibility was confirmed by Fourier transform infrared spectroscopy (FTIR) and Differential scanning calorimeter (DSC) studies. FDT retained its crystalline nature after tableting which was revealed by X-ray Diffraction studies. The disintegration time (DT) of the optimized formulation F1 (150 mg strength) and F2 (500 mg) showed rapid DT of 9 and 14 s when carried out using 1 mL purified water. FDTs demonstrated excellent *in vitro* dissolution results. Stability studies results were also found satisfactory when stored at 25 ± 2 ° C / 60 ± 5% RH. Hence it can be concluded that CAP FDT disintegrates rapidly in seconds with excellent dissolution profile, thus providing convenience of administration, patient compliance and safety to overcome swallowing problem for dysphagia patients.

Keywords: Fast dissolving tablet; Polymeric based Superdisintegrants; Dysphagia patients; Capecitabine; Cancer

INTRODUCTION

The oral route is the most preferred route in the administration of medicinal products and drug therapy. However dosage form such as tablets, capsules, liquids which are used orally are difficult to swallow in case of dysphagia patients. Dysphagia is a clinical syndrome resulting from a biomechanical disorder which is defined as 'an inability to swallow, or a sensation that solids or liquids do not pass easily from the mouth to the stomach'. Swallowing disorders (dysphagia) occur in all age groups, preterm babies to the elderly (Dixit et al., 2011). Crushing tablets and opening capsules are the main alterations of dosage forms and account for up to one third of oral drug administrations in long-term nursing homes. Such alterations may lead to serious adverse effects or severe intoxication of the patients (Cornish, 2005).

Higher incidence of non-communicable diseases, especially cancer is associated with percentage of aged population of a country. It is predicted that the elderly population of India shall be among the highest in the world by the year 2025, i.e. 177 million (80 % of them residing in rural areas) (Marimuthu, 2008). Breast carcinoma has become a major health problem over the past 50 years, affecting as many as one in eight women (Harding, 2012). Colorectal cancer is the second leading cause of cancer deaths in the West and more than 66 000 cases of colon cancer are reported to occur in the Indian subcontinent every year (Sinha et al., 2010). The oral fluoropyrimidine CAP has been investigated extensively in both metastatic colorectal cancer and metastatic breast cancer. It is widely used in the treatment of metastatic colorectal cancer and breast cancer, since it is readily absorbed from the gastrointestinal tract. The recommended oral daily dose is large, i.e. 1250 mg/m^2 administered twice daily for 14 days followed by a 7-day rest period given as 3-week cycles, for as long as needed. Indeed, after oral administration, CAP crosses the gastrointestinal barrier intact and is rapidly and almost completely absorbed (Judson et al., 1999). Due to high dose, around 3 to 7 tablets are swallowed each time. Due to increased frequency of administration, the conventional tablet may be difficult to swallow by dysphagic patients. Hence in the present research work, new pharmaceutical dosage form such as fast disintegrating tablet was prepared and evaluated to ensure safety during oral administra-

* Corresponding Author
Email: dixit_life2006@rediffmail.com
Contact: +91-9986428939
Received on: 31-08-2012
Revised on: 22-09-2012
Accepted on: 25-09-2012

Table 1: Composition of optimized capecitabine FDT

Formulation ingredients (mg)	F1	F2
Drug	150	500
Crospovidone	17.5 (5 %)	47.5 (5 %)
Neusilin	28 (8 %)	28.5 (3 %)
PVP K 30	17.5 (5 %)	66.5 (7 %)
Sucralose	5.7	5.7
Strawberry flavor	12	12
Magnesium stearate	7 (2%)	19 (2 %)
Mannitol Q.S to	350 mg	950 mg

tion of medications and thereby improving patient compliance.

FDTs are defined as a solid dosage form containing medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue'. The disintegration time for FDTs generally ranges from several seconds to about a minute (Abed et al., 2010).

MATERIALS AND METHODS

CAP was obtained as gift sample by Dr. Reddy's Laboratories (Hyderabad, India). Crospovidone (CP) was obtained as a gift sample by Micro Labs (Bangalore, India). Mannitol GR was procured from Lobachemie Pvt. Ltd. (Mumbai, India). Croscarmellose Sodium (CCS) and Sodium Starch Glycolate (SSG) were gifted by Malpe biotech Pvt. Ltd. (Pune, India). Neusilin US2 was gifted by Fuji Chemical Industry (Toyama, Japan). Sucralose was kindly gifted by J.K. Sucralose India Ltd. (Delhi, India). All other chemicals and reagents used were of analytical grade.

Preparation of FDT

Orally disintegrating tablets containing CAP and different concentrations of superdisintegrants were prepared by wet granulation technique. The raw materials were passed through sieve no. 100 prior to mixing. Drug, intragranular fraction (50 %) of superdisintegrants, mannitol and neusilin were weighed and mixed thoroughly by geometric dilution. Water solution of PVP (w/v) was added to the mixture in a quantity enough to prepare the wet mass. The wet mass was granulated using sieve no. 44/100, dried in a tray dryer at 35 °C. The dried granules were mixed with extragranular fraction (50 %) of superdisintegrants, mannitol, neusilin and required proportion of fines (10 %). Sweetener and flavor were added to the granules with mixing. Finally the granules were lubricated with magnesium stearate and punched into tablets using a 16 station tablet punching machine (Rimek, Ahmedabad, India) (Sheshala et al., 2011). The composition of optimized FDT formulation is shown in Table 1.

FT – IR Spectroscopy

Drug:excipient mixture was mixed with Potassium bromide in the ratio of 1:100, triturated and compressed to prepare the pellet. Twenty scans were acquired in the 4000 – 600 cm^{-1} range with a resolution of 4 cm^{-1} using FT-IR spectrophotometer (Shimadzu, 8400S, Japan). FT-IR spectrum of mixture was compared with that of plain drug (Kulkarni et al., 2012).

CAP analytical method

A reverse phase HPLC method was used for the quantification of CAP as described by Pani et al. (2011). The integrated HPLC system (SHIMADZU LC-2010A HT, Kyoto, Japan) equipped with low pressure quaternary pump along with dual wavelength UV detector (SPD-20A), and auto sampler has been used for the analysis. The chromatographic separation was achieved with phenomenex luna 5µ C8 (2) 100A column (250 X 4.60 mm i.d., 5 µm particle size). Calibration standard solutions were prepared from stock solution (1 mg/mL) by sequential dilution with mobile phase to yield final concentration of 0.5 - 64 µg/mL (n=6). A calibration curve was constructed by plotting the peak area on ordinate as a function of CAP concentration on abscissa. The method was validated to ensure performance of the chromatographic method as per International Conference on Harmonization (ICH), for the parameter precision and accuracy.

Pre and post compression evaluations

The precompression properties such as bulk and tapped density (Electrolab Density Tester ETD – 1020), true density, angle of repose, Carr's index, hausner ratio, porosity and post compression properties like hardness (Pfizer Digital Hardness tester), friability (Electrolab EF - 2 Friabilator), weight variation and content of the compressed tablets were determined as per standard procedures (USP 35-NF 30, 2012).

Wetting time and water absorption ratio

A piece of tissue paper (12×10.75 cm) folded twice was placed in a Petri dish (internal diameter of 9 cm) containing 10 mL of buffer solution (pH 6.8) simulated saliva and amaranth (dye). A tablet was carefully placed on the surface of the tissue paper with the help of forceps and the time required for the dye to reach the upper surface of the tablet was recorded as wetting time. The wetted tablet was then weighed. Water absorption ratio 'R' was calculated using the equation:

$$R=100 \times (W_b–W_a)/W_a$$

Table 2: Physical characteristics of optimized formulations of capecitabine FDT. Values are expressed as mean ± SD; n = 6

Evaluation Parameters	150 mg dose tablet (F1)	500 mg dose tablet (F2)
Angle of repose (°)	25.08 ± 1.51	27.1 ± 2.0
Bulk density (g/mL)	0.453 ± 0.10	0.469 ± 0.09
Tapped density (g/mL)	0.510 ± 0.08	0.535 ± 0.10
True density (g/mL)	3.12 ± 0.09	3.44 ± 0.12
Hausner ratio	1.125 ± 0.12	1.140 ± 0.15
Porosity (%)	85.48 ± 1.12	86.36 ± 1.85
Carr's index (%)	11.1 ± 1.5	12.33 ± 1.7
Drug content (%)	97. 9 ± 1.7	98.1 ± 2.4
Weight variation	147 ± 2.5	498 ± 3.3
Hardness (kg/cm^2)	3.64 ± 0.2	3.66 ± 0.25
Friability %	0.280 ± 0.040	0.302 ± 0.051
In vitro Disintegration time (s)		
Method A	6.0 ± 1.24	9.12 ± 1.10
Method B	9.08 ± 1.5	14.1 ± 1.8
Wetting time (s)	14.05 ± 1.11	20.1 ± 1.07
Water absorption ratio (%)	87.9 ± 1.0	83.6 ± 1.12

Where 'W_a' is weight of tablet before water absorption and 'W_b' is weight of tablet after water absorption (Khalid, 2010; Arya and Chandra, 2010).

In vitro disintegration time

In vitro disintegration time of the tablets was evaluated using 2 different methods (Shukla et al., 2009).

A. Conventional disintegration apparatus-basket rack assembly (as mentioned in Indian pharmacopeia) was used to check the DT of the tablets. Distilled water was used as disintegrating medium. The basket-rack assembly is rigid and supports six cylindrical glass tubes. The volume of medium was 900 mL maintained at 37 ± 0.5 °C.

B. Disintegration test was conducted by placing the fast dissolving tablet in a glass cylinder fitted with 10 mesh at its base. This set up was further placed in a shaking water bath operated at 150 rpm. 1 mL of purified water maintained at 37 °C temperature was used as medium. The critical parameters of this method were the operational speed of shaking water bath and volume of the medium.

Thermogravimetric Analysis (TGA) and DSC studies

The thermal analyses of the samples were carried out using thermogravimetry (SDT Q600, TA Instruments, USA). Samples (~ 5 mg) were placed in an aluminum crucible cell which was firmly crimped to provide an adequate seal. The analysis was done under purge of dry nitrogen gas at a flow rate of 100 mL/min. The DSC of the drug and optimized tablet was performed by heating it from ambient temperature to 250 °C with heating rate of 10 °C/min. The change in mass of a sample, as the sample is heated was measured using TGA. TGA of the sample was carried out by heating from ambient temperature to 500 °C with heating rate of 10 °C/min. The analysis was done under purge of dry nitrogen gas at a flow rate of 100 mL/min.

XRD studies

XRD analysis of optimized tablet in comparison with pure drug and placebo, was performed using Rigaku Miniflex II desktop X-Ray diffractometer (Japan) with a monochromator addition that captures X-rays other than Cu Kα for use in analysis. The samples were scanned over a 2θ range of 3° to 57° at a scan speed of 10°/min and a step size of 0.01°.

Dissolution studies

Dissolution studies of the optimized tablet F1, F2 and plain drug (equivalent dose) were performed using USP dissolution paddle apparatus (Electrolab TDT 08L, Mumbai, India). The dissolution studies were carried out with a stirring speed of 50 RPM at 37 ± 0.5 ºC using three different buffer systems (pH 1.2, pH 4.5 acetate buffer and pH 6.8 phosphate buffer) of 900 mL. Two milliliters aliquots of dissolution media were collected at predetermined time intervals and replaced with equal volumes of respective buffer. The collected samples were filtered through 0.22 µm millipore filter and the concentration of the dissolved CAP was determined using the HPLC technique. Dissolution profile of tablet formulation was compared with that of the plain drug (n = 6). The data obtained were statistically analyzed using one way analysis of variance ($p < 0.05$).

Stability studies

Stability studies were carried out on optimized tablets by storing them at 25 ± 2 ° C / 60 ± 5% RH and 40 ± 2 ° C / 75 ± 5% RH for 6 months in stability chambers (Thermolab humidity chambers, India). Samples were analyzed at the intervals of one month for various parameters such as hardness, drug content, disintegra-

tion time and *in vitro* drug release. The results were the average of six determinations. The release studies were statistically evaluated using one way analysis of variance ($P < 0.05$).

RESULTS

Formulation of FDT is a challenging task since the formulator should select raw materials which have a quick disintegration rate in the mouth and a high compressibility in order to yield an adequate hardness when compressed. Hence preliminary trails were carried out to prepare FDT by varying the concentration of superdisintegrants, neusilin and magnesium stearate to obtain desired tableting property.

The primary requirement of FDT is faster disintegration which precedes drug dissolution. Superdisintegrants such as CCS, SSG and CP are frequently used in tablet formulations to improve the rate of tablet disintegration and thus improve the rate of drug dissolution. Hence initially tablets were optimized for shorter DT using SSG (2 – 8 %), CCS (0.5 – 5 %) and CP (2 – 5 %) (Rowe et al., 2009). Tablets were prepared using various concentrations of superdisintegrants with a constant hardness of 3.65 ± 0.05 kg/cm^2. Disintegration study was carried out using method 'A', with 900 mL of dissolution medium. The DT for tablets (150 mg and 500 mg strengths) prepared using SSG (2, 4, 6 and 8 %) ranged from 59 to 135 s whereas DT for CCS (0.5, 1.5, 2.5, 3.5, 4.5 and 5.0 %) ranged from 26.0 to 75 s and DT of the tablets prepared using CP (1, 2, 3, 4 and 5 %) ranged from 6 sec to 37 s. The difference in DT between different superdisintegrants can be attributed to the difference in nature and mechanism of individual superdisintegrants. The results of DT obtained by various superdisintegrants are graphically presented in Figure 1. From the graph it is clear that, increase in concentration of CCS (up to 2.5 %) and SSG (up to 4 %) showed positive effect on DT i.e. DT decreased; later increase in concentration of these superdisintegrants had a negative effect on DT of the tablets; however CP had a positive effect on the disintegration of tablets with increasing concentration. It was found that formulation prepared using CP showed faster DT than CCS and SSG. This is due to the formation of a viscous gel layer by CCS and SSG which might have formed a thick barrier to the further penetration of the disintegrating medium and hindered the disintegration or leakage of tablet contents (Setty et al., 2008). The obtained results were similar to the finding of Pandya et al., 2009 in which preparation of fast dissolve tablet of celecoxib showed decrease in DT up to certain concentration of CCS, however further increase had negative effect on DT. CCS even though it is water insoluble it still contains water soluble contents (6 %), which becomes viscous and adhesive when hydrated. When CCS was added to the tablet at higher concentration, absorption of water may cause increase in the viscosity of liquid within tablet and may delay further penetration of water (Bi et al., 1999). Another drawback encountered by SSG during the preparation of granules is that, increase in concentration of SSG tends to stick to each other which may be due to gel formation of SSG on contact with water. Increasing the concentration of CP (1 to 5 %) resulted in faster disintegration of tablets, which may be due to a rapid capillary activity and pronounced hydration with little tendency for gel formation (Setty et al., 2008). From the above discussion it was clear that crospovidone was significantly superior (showed shorter DT) compared to the other superdisintegrants tested.

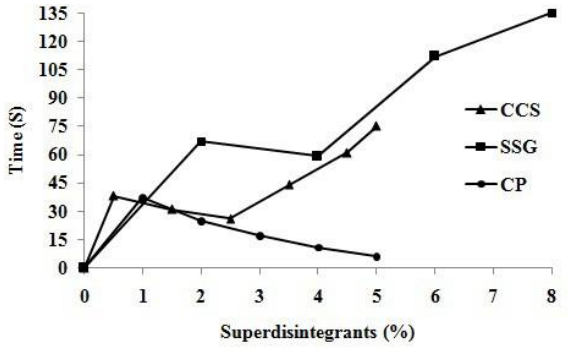

Figure 1: Results of disintegration time of superdisintegrants (CCS, CP and SSG) carried out using conventional disintegration apparatus-basket rack assembly (Method 'A')

Neusilin had positive effect on disintegration of the tablet. DT decreased by increasing the concentration of neusilin which may be due to its large surface area and porous nature which tend to adsorb high amount of water and mechanically compacted into high quality tablets (Neusilin US2, 2007). Neusilin even had a positive impact on flow property. However they showed a drawback; when high concentration of neusilin (> than 8 % & 3 % for 150 mg and 500 mg strength respectively) was used, they caused ejection of the blend from the die during compression which may be due to density of neusilin. Neusilin concentrations were adjusted such that it favored good flow without any ejection of blend from the die during compression. Interestingly it was found that neusilin with CP showed shorter disintegration time than other superdisintegrants used. Hence in the present study tablets prepared using neusilin showed excellent disintegrant and glidant property.

Concentration of magnesium stearate was optimized such that it there was no sticking of granules onto the punches and produced shorter DT. DT increased with increased concentration of magnesium stearate. DT increased from 6 to 10 s and 9 to 15 s with increased concentration of magnesium stearate from 2 to 3 % for 150 and 500 mg strength respectively. The results obtained in the present study were in agreement with the findings of Late et al. (2009) where DT increased with increase in concentration of magnesium stearate. This delayed disintegration is due to the general agreed observation that magnesium stearate forms a hydro-

phobic membrane on the surface of the powder particles. Hence, optimum lubricant concentration of 2 % was finalized which not only circumvent picking and sticking but also favors decrease in DT of the tablet.

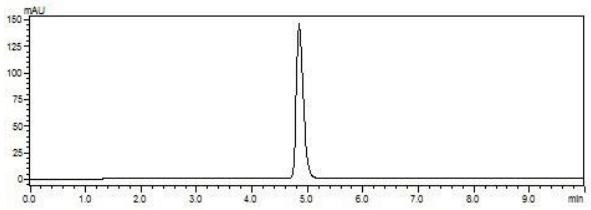

Figure 2: Typical chromatograms of standard CAP

The characteristic peaks of physical mixture of drug with excipients were compared with peaks obtained from pure drug (Figure no provided). Bands appearing at 3432 cm^{-1} 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 cm^{-1} and 1756 cm^{-1} are due to urethane carbonyl stretching vibrations. Characteristic bands at 1042 cm^{-1} and 1202 cm^{-1} indicate C–F stretching vibrations as well as the presence of tetrahydrofuran ring respectively (Agnihotri and Aminabhavi, 2006). Wave numbers present in the IR spectra of CAP were also found in the physical mixtures with corresponding intensities attributing to the compatibility of drug-excipients.

The analytical method used for CAP estimation showed retention time of 4.849 ± 0.008 min. Typical chromatograms of standard CAP is shown in Figure 2. A good linear relationship was observed between the standard concentration range of 0.5 – 64.0 µg/mL (r^2 = 0.9998; n=6). The LLOQ i.e., the lowest concentration on the calibration curve that could quantify CAP with acceptable precision and accuracy was 0.0125µg/mL. The accuracy at the low (0.5 µg/ml), moderate (4.0 µg/mL) and higher (64.0 µg/mL) concentrations of CAP ranged from 97.4 to 100.5 % and 95.8 to 101.5 % for intra-day and inter-day estimations respectively (n = 6 for each concentrations). The precision of the aforesaid low, moderate and higher concentration expressed as % C.V was found to be less than 6 % for intra-day assay and less than 8 % for inter-day assay indicating that % C.V was within the limits (% C.V. had to be within 20% for the lowest concentration and 15% for the upper levels).

The pre-compression and post-compression values of the optimized tablets (F1 and F2) were tabulated in Table 2. Angle of repose indicates gross measurements of the flowability of powders. Granules of formulation F1 and F2 showed excellent flow property as the values were within 30 ° (USP 35-NF 30, 2012). The compressibility index and the closely related hausner ratio have become the simple, fast and popular methods of predicting powder flow characteristics. As the values of carr's index increase, the flow of powder decreases. F1 and F2 showed carr's indices of 11.1 and 12.33 % and hausner ratio of 1.125 and 1.140 indicating good flow character of the granules and hence easily compressible (USP 35-NF 30, 2012). F1 and F2 formulations had very good porosities of 85.48 and 86.36 % respectively. The obtained tablets were spherical in shape with smooth surface. As the powder mixture was free flowing, tablets produced were of uniform weight with acceptable weight variation (percent weight within the pharmacopeia limits of ± 7.5 % of the average weight) (Khalid et al., 2010). The drug content accessed by HPLC for F1 and F2 formulation were 97.9 and 98.1 % indicating drug has uniformly distributed in the tablets. The hardness of the F1 and F2 tablets was 3.64 and 3.66 kg/cm^2 which indicate that FDT had optimum mechanical strength. Another measure of a tablet's strength is friability. The friability of the tablets was within the compendial limits (<1 %), which depicts that the optimized formulations can withstand abrasion during handling, packaging and shipment (USP 35-NF 30, 2012).

Wetting time is closely related to the inner structure of the tablets and to the hydrophilicity of the excipient. The wetting test uses minimal water which may be representative of the quantity of saliva available orally (Patil and Das, 2011). Wetting time for F1 and F2 (Table 2) tablets were 14.05 and 20.1 s and water absorption ratio was 87.9 and 83.6 % respectively. Wetting time & water absorption ratio of tablets was excellent may be due to neusilin and/ or due to superdisintegrant (CP) used which intake water by capillary action.

According to US FDA specification, the disintegration time of FDT should not exceed 30 s. Various researchers have used different methods to determine the time taken for the tablet to disintegrate. Hence an attempt was made to carryout disintegration studies by using two different methods. *In Vitro* disintegration time of F1 and F2 tablets were 6.0 s and 9.12 s when determined using conventional disintegration-basket rack assembly (Method 'A') and DT of F1 and F2 showed DT of 9.08 s and 14.1 s when determined using method 'B' respectively. Method A was carried out using conventional disintegration-basket rack assembly as per USP. Method 'B' was carried out since the conventional test employs a relatively huge volume of test solution (900 mL) compared to the volume of saliva in human buccal cavity, which is less than 6 ml [Shukla et al., 2009]. Therefore, the results obtained from the conventional disintegration test may not reflect the actual disintegration rate in the human mouth. From the results, it was found that there was no significant difference in the DT of the formulation due to change in methods (Table 2). As discussed earlier it is due to nature of the superdisintegrant (CP) and neusilin which favored faster disintegration of the tablets. Neusilin due to its high water absorptive nature and CP due to its capillary action allows rapid water penetration throughout the tablet thereby favoring rupture and complete disintegration of the tablet.

DSC thermogram of CAP and optimized FDT are presented in Figure 3. DSC thermogram of CAP (A) showed a sharp melting endothermic peak at 124.19 °C which corresponds to the melting point of the drug. This result is in agreement with the result obtained by Agnihotri and Aminabhavi (2006) where melting point of CAP was 122 °C. In case of DSC thermogram of tablet (B); two endothermic peaks were observed, one at 124.98 °C which corresponds to melting point of the drug and other at 164.96 °C which may be due to excipient used in the formulation. The melting peak of excipient might me due to mannitol which has a melting point range of 164 – 169 °C. Drug endothermic peak retained at 124.98 °C in the formulated tablet indicates that there was no interaction between drug and excipients.

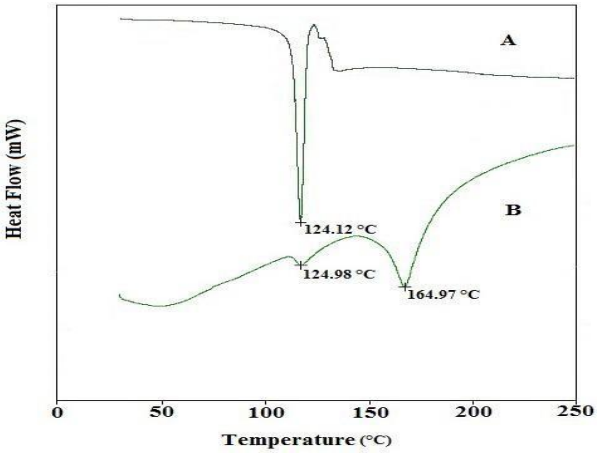

Figure 3: DSC thermogram of CAP (A) and optimized FDT (B)

TGA measures the amount of weight change of a material, either as a function of increasing temperature, or isothermally as a function of time, in an atmosphere of nitrogen. The % weight change of optimized tablet is depicted in Figure 4. Form the figure it revealed that, less than 3 % weight reduction was seen below 100 °C which may be due to evaporation of moisture; from this it was clear that the moisture content in the tablet was very low and within the acceptable USP limits (USP 35-NF 30, 2012). A secondary curve with decrease in weight (± 5 %) was observed at 124.19 °C which may be due to melting of the CAP. The major weight loss (± 65 %) transition occurred between 220 °C to 320 °C (shoulder peak) which can be imputed due to decomposition of more than one material. The final weight loss transition with saturation occurred after 450 °C indicating complete degradation of film formulation. The final weight of 21.46 % after 480 °C was seen with saturation and hence continuation of the heating was terminated.

Crystallinity of compound is indicated by the presence of sharp peaks that remains absent in case of amorphous compounds. X-ray diffraction patterns of optimized FDT formulation, placebo tablet and pure drug (CAP) are shown in Figure 5. The X-ray diffraction pattern of CAP showed peaks which are consistent with the results obtained by Agnihotri and Aminabhavi (2006). The pattern of CAP (C) displayed intense and sharp peaks at 2 θ of 5°, 20° and 25° confirming its crystalline nature. On the contrary, the FDT (B) was characterized by a consistent pattern as that of plain drug indicating no interaction took place during manufacturing of tablet. From the placebo tablet diffraction pattern (A), it is clear that it lack drug peaks but retained other peaks which were seen in FDT (B).

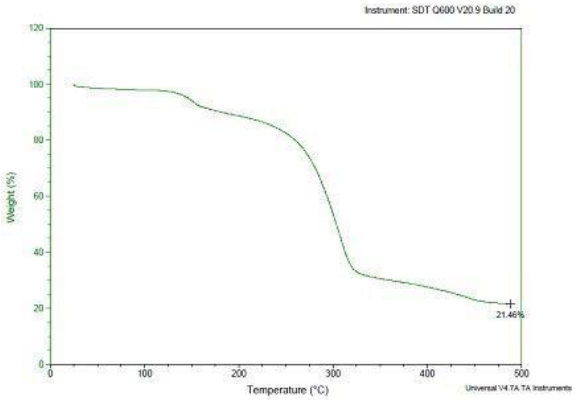

Figure 4: TGA thermogram of optimized tablet

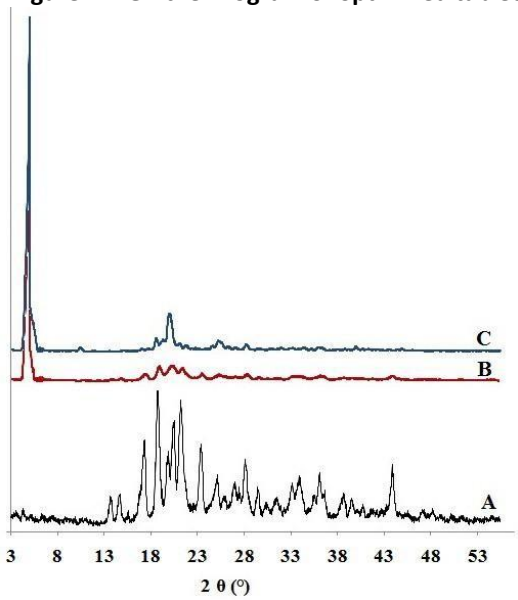

Figure 5: X-ray diffraction patterns of placebo tablet (A), optimized FDT (B), and pure drug (C)

The dissolution studies of F1 and F2 FDT were conducted using bio-relevant media; simulated saliva (pH 6.8), simulated gastric fluid (0.1N HCl) and pH 4.5 acetate buffer as absorption of drug from the tablet can occur through buccal, sublingual mucosa, oropharyngeal, esophagus, and stomach. The *in vitro* dissolution profiles of F1 and F2 CAP FDT compared with plain drug are depicted in Figure 6 and Figure 7 respectively. Dissolution was compared with the plain drug to get an insight of release of the drug from tablets. From the plot (Figure 6) it was found that, at all pH medium ~ 98 % of drug was released from F1 tablet (150 mg strength) and plain drug (150 mg) within 180 sec. The results obtained from F2 tablet was similar to that of F1 tablet, However it took more time to release

the drug. From the plot (Figure 7) it was found that, at all pH medium ~ 95 % of drug was released from F2 tablet (500 mg strength) and plain drug (500 mg) within 240 sec. There was slight difference seen in the release between tablet and plain drug (more than FDT) at various pH medium due to fact that plain drug is readily available in the dissolution medium whereas FDT has to initially disintegrate first and later release the drug, however the difference was not statistically significant ($p < 0.05$). This faster dissolution of F1 and F2 FDTs was mainly due to disintegrants used in the tablet. Disintegrating agent accelerates tablet disintegration into smaller fragments increasing the surface area exposing to the medium for dissolution of the drug to occur.

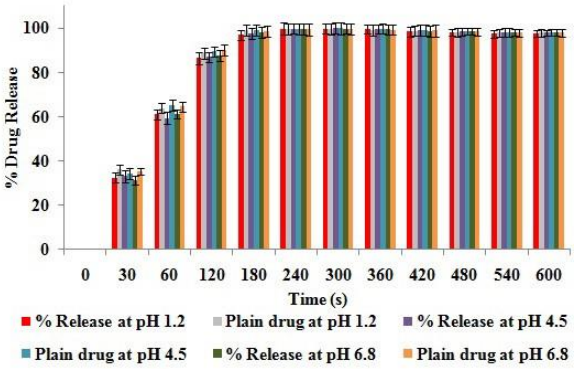

Figure 6: *In vitro* drug release profile of F1 FDT and plain drug (CAP) at pH 1.2, 4.5 and 6.8. Error bars indicate the standard deviation (n = 6)

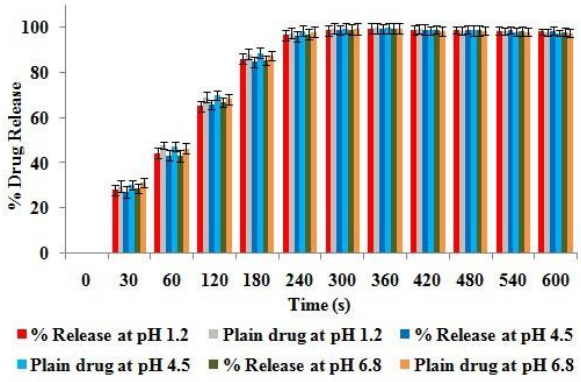

Figure 7: *In vitro* drug release profile of F2 FDT and plain drug (CAP) at pH 1.2, 4.5 and 6.8. Error bars indicate the standard deviation (n = 6)

When the FDT was stored at normal temperature (25 ± 2 ° C / 60 ± 5% RH) for 4 - 24 weeks; no apparent change in form, color (observed visually), hardness, content (96.1 ± 1.6 %), DT and release was reported in F1 and F2 tablets. The results of drug release carried out for 6 months for F1 and F2 tablet at any pH medium were in the range of 94.5 % to 99.2 % (180 s) and 90.1 % to 99.5 % (240 s) respectively, whereas the release of plain drug (150 mg and 500 mg) ranged from 95.6 to 99.5 % (180 s) and 91.7 to 99.1 % (240 s) respectively. At accelerated temperature (40 ± 2 °C/75 ± 5% % RH); the tablet tend to change its form (softened) and color (dull) at sixth month sampling. Hardness and DT decreased significantly indicating that tablets have lost their mechanical integrity. There was significant change ($p < 0.05$) in content (76.9 ± 2.0 %) and drug release (data not provided) observed at sixth month sampling. The overall results suggest that, CAP ODT should be stored at normal temperature (25 ± 2 ° C / 60 ± 5% RH) with proper packing.

CONCLUSION

From the preliminary study, it revealed that fast-disintegrating tablets of capecitabine were successfully prepared by wet granulation technique using CP (superdisintegrant), neusilin (disintegrant & glidant) and magnesium stearate (lubricant). Amongst various formulation prepared, tablets containing 5 % CP (for F1 and F2), 8 % (for F1) & 3 % (for F2) neusilin and 2% magnesium stearate (for F1 & F2) was considered optimized. The produced tablet showed smooth surface without any interactions between drug and excipients as confirmed by DSC analysis. The optimized formulae (F1 and F2) showed satisfactory pre & post compression properties, satisfactory physical resistance, shortest *in vitro* disintegration time and with excellent dissolution profile. Stability studies revealed that FDT formulation should be stored at normal temperature (25 ± 2 ° C / 60 ± 5% RH). These findings suggest that the present oral fast disintegrating tablet containing CAP provides better compliance for dysphagic and elderly patients, who inherently pose a hurdle in administering conventional oral medication.

ACKNOWLEDGEMENTS

Authors would like to thank University Grants Commission, New Delhi, India for its financial support to major research project.

REFERENCES

Abed, K.K., Hussein, A.A., Ghareeb, M.M., Abdulrasool, A.A., 2010. Formulation and optimization of orodispersible tablets of diazepam. AAPS PharmaSci Tech. 11, 356-361.

Agnihotri, S.A., Aminabhavi, T.M., 2006. Novel interpenetrating network chitosan-poly(ethylene oxide-g-acrylamide) hydrogel microspheres for the controlled release of capecitabine. Int. J. Pharm. 324, 103-115.

Arya, A., Chandra, A., 2010. Fast drug delivery systems: A Review. Der Pharmacia Lettre 2, 350-361.

Bi, Y.X., Sunada, H., Yonezawa, Y., Danjo, K., 1999. Evaluation of rapid disintegrating tablets prepared by a direct compression method. Drug Dev. Ind. Pharma. 25, 571-581.

Cornish, P., 2005. Avoid the crush: hazards of medication administration in patients with dysphagia or a feeding tube. CMAJ 172, 871-872.

Dixit, A.S., Parthasarathi, P.K., Hosakote, G.S., 2011. Gels and jellies as a dosage form for dysphagia patients: A Review. Curr. Drug Ther. 6, 79-86.

Harding, F., Breast cancer: Cause – Prevention - Cure. Available at: http://books.google.co.in/ books?id=0h2gDLv3MOEC&printsec=frontcover&source=gbs_ge_summary_r&cad=0#v=onepage&q&f=false [Accessed on 1 July 2012].

Judson, I.R., Beale, P.J., Trigo, J.M., Aherne, W., Crompton, T., Jones D., Bush, E., Reigner, B.A., 1999. Human capecitabine excretion balance and pharmacokinetic study after administration of a single oral dose of 14C-labelled drug. Invest. New Drugs 17, 49-56.

Khalid, K.A., Hussein, A.A., Ghareeb, M.M., Abdulrasool, A.A., 2010. Formulation and optimization of orodispersible tablets of diazepam. AAPS PharmSciTech. 11, 356-361.

Kulkarni, P.K., Dixit, A.S., Singh, B.S., 2012. Evaluation of bacterial cellulose produced from Acetobacter xylinum as pharmaceutical excipient. Amer. J. Drug Disc. Dev. 2, 72-86.

Late, S.G., Yu, Yi-Ying., Banga, A.K., 2009. Effects of disintegration-promoting agent, lubricants and moisture treatment on optimized fast disintegrating tablets. Int. J. Pharm. 365, 4-11.

Marimuthu, P., 2008. Projection of cancer incidence in five cities and cancer mortality in India. Indian J. Cancer 45, 4-7.

Neusilin US2 2007. The extraordinary excipient for solid dosage forms. Technical newsletter/Nov. Available at: http://www.fujichemical.co.jp/english/newsletter/newsletter_pharma_0711.html [Accessed on 21 May 2011].

Pandya, V.M., Patel, D.J., Patel, J.K., Patel, R.P., 2009. Formulation, characterization, and optimization of fast-dissolve tablets containing celecoxib solid dispersion. Dissolut. Technol. 16, 22-27.

Pani, K.A.D., Venkata, R.Y., Sunitha, G., Rama, K.K., Ceema, M., Rao, V.A., 2011. Development of Validated Stability Indicating RP-HPLC Method for the estimation of capecitabine in Pure and Pharmaceutical Formulations. Int. J. Res. Pharm. Biomed. Res. 2, 175-181.

Patil, C., Das, S., 2011. Effect of various superdisintegrants on the drug release profile and disintegration time of lamotrigine orally disintegrating tablets. Afr. J. Pharm. Pharacol. 5, 76-82.

Rowe. R.C., Sheskey. P.J., Quinn, M.E., 2009. Handbook of pharmaceutical excipients, 5th ed. Pharmaceutical Press, London.

Setty, C.M., Prasad, D.V.K., Gupta, V.R.M., Sa, B., 2008. Development of fast dispersible aceclofenac tablets: Effect of functionality of superdisintegrants. Indian J. Pharm. Sci. 70, 180-185.

Sheshala, R., Khan, N., Chitneni, M., Darwis, Y., 2011. Formulation and In vivo evaluation of ondansetron orally disintegrating tablets using different superdisintegrants. Arch. Pharm. Res. 34, 1945-1955.

Shukla, D., Chakraborty, S., Singh, S., Mishra, B., 2009. Mouth Dissolving Tablets II: An overview of evaluation techniques. Sci. Pharm. 77, 327–341.

Sinha, V.R., Aggarwal, A., Srivastava, S., Goel, H., 2010. Influence of operational variables in multiparticulate delayed release systems for colon-targeted drug delivery of celecoxib using extrusion spheronization. Asian J. Pharm. 4, 102-109.

U.S. Food and drug administration, Guidance for industry orally disintegrating tablets. 2008. Available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070578.pdf [Accessed on: 15 Feb 2012].