Excellence In Research Work For Which The Sun Pharma Research Award Is Claimed

Formulation, Development and In vitro Characterization of Modified Release Tablets of Capecitabine

Abstract

Objective: The main aim of this research work was to develop and evaluate cost effective modified release tablets of Capecitabine (CAP) without utilizing coating techniques.

Methods: The tablets were prepared by non-aqueous wet granulation method. Hydroxypropyl cellulose (HPC) was used as a extended release matrix former and sodium alginate (SA) was used as sustained release agent due to its gel forming ability. 3^2 full factorial design was used to study the effect of the independent variables i.e. HPC and SA on dependent variables, *in vitro* drug release and swelling index. The physiochemical properties of the drug were analyzed by ultraviolet (UV), fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC) and powder X-ray diffraction (P-XRD). The formulated tablets were evaluated for hardness, thickness, weight variation, content uniformity, swelling index, and *in vitro* drug release study.

Results: The FTIR and DSC studies confirmed that there was no any interaction between drug, polymers and excipients. Also from DSC and P-XRD studies it was clear that the crystalline nature of CAP was remain unchanged in the optimized formulation tablet. Formulation F8 retarded the drug release up to 24 h with the optimum concentration of the both the polymers.

Conclusion: We have successfully developed the modified release tablets of CAP with the combination of diffusion and erosion controlled type of drug release mechanism.

Keywords: Modified release; Capecitabine; GIT cancer; Hydroxypropyl cellulose; Sodium alginate

1. Introduction

Cancer of digestive tract (GIT cancer) is the most common malignant tumour which is the life threatening disease in the health of human beings [1]. Cancer is one of the leading causes of morbidity and mortality worldwide with approximately 14 million cases in 2012 [2]. It is the second most leading cause globally, responsible for about 8.8 million deaths in 2015. Due to the cancer 70% of deaths occur in low and middle income countries [3]. Various treatments are available for the cancer which includes combination of chemotherapy, radiotherapy and immunotherapy [4]. The Capecitabine (CAP) is an anti-cancer drug used in the treatment of GIT as well as metastatic breast cancer, colorectal cancer, and oesophageal cancer [1, 4, 5]. It is a prodrug which is enzymatically converted to 5-flurouracil (5-FU) in the body at the tumour site [1, 5, 6]. It has short elimination half-life of about 0.5-1 h [4, 7, 8].

The oral route for delivering the medications is the most preferred route because of patient compliance, easy for administration accurate dosing, cost-effective manufacturing methods, and improved shelf life of the product. Conventional oral dosage forms releases the drug rapidly after administration and faster absorption into the body from GIT. Conventional immediate release (IR) tablet dosage forms do not maintain the plasma levels of the drug within the therapeutic range for an extended period of time, therefore short duration of action may be observed. Also IR formulations required multiple dosing [9]. Modified release drug delivery systems are designed to achieve a prolonged therapeutic effect over an extended period of time after administration of a single dose [10]. Advantages of modified release dosage forms over the conventional dosage forms includes: [9-12].

- Due to less frequent drug administration patient compliance as well as patient convenience is improved.
- Better control of plasma levels which increases the safety margin of high potency drugs.
- Reduces the fluctuations in blood concentrations of conventional drug delivery.
- Minimize the local as well as systemic side effects.
- Reduces the total amount of drug to be administered.

The main objective of this research work is to develop the device which is not only target the drug release in colon but also prevent it from releasing in the upper part of GIT. Routinely the coating technology is used to achieve this objective but this technology having some drawbacks. In coating technology organic solvents are mostly used it is flammable and toxic. The risk of toxicity is due to the residual solvents in a device. In case of aqueous film coating heat requirement and prolong drying period will increase the manufacturing cost is major disadvantage. Therefore the modified release tablets of CAP as a model drug, was developed by using hydroxypropyl cellulose (HPC) as a extended release matrix former and sodium alginate (SA) as release modifying polymer [13,14]. The SA used in preparations of sustained release oral formulations as it can delay the dissolution of a drug from the tablets, capsules, and aqueous suspensions [13]. Hence the modified release tablets of CAP were developed by using HPC and SA in different concentrations. The HPC was used in concentration between 20-30% w/w with the optimum concentration of about 25% w/w for extended drug release. The SA was used in concentration between 21-25% w/w with the optimum concentration of about 23% w/w [14]. Alginate shrinks and the drug is not released at low pH of the gastric environment [15, 16]. The pH sensitivity of SA affect the characteristics of the diffusion barrier and the drug release [16]. The main objective of this system was to prolong the drug release and to improve the bioavailability of CAP with reduction in dosing frequency (due to its shorter elimination half-life, i.e. 0.5-1 h) as well as reduction in dose related side effects and development of this cost effective system without the use of enteric coating polymers. We have studied the different physicochemical properties of CAP by using the various advanced analytical techniques such as ultraviolet (UV) spectroscopy, Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), and powder X-ray diffraction (P-XRD). Further, we have investigated the effect of types of polymers, concentration of polymers and combination of the HPC and SA on % drug release and swelling index of the prepared formulations.

2. Materials and methods

2.1 Materials

The CAP was obtained as a gift sample from Cipla Ltd., Vikhroli, Mumbai. The HPC, SA, Lactose, Magnesium stearate and isopropyl alcohol were obtained from Loba Chemie Laboratory Reagents and Chemicals. All other reagents and chemicals used were of analytical grade.

2.2 Methods

2.2.1 Preformulation study

2.2.1.1 Melting point

The melting point determination gives idea about the purity of the compound. Melting points of CAP, HPC, SA, Lactose, and Magnesium stearate were determined by using the capillary method [17-19].

2.2.1.2 Solubility

The solubility of CAP was determined by addition of an excess amount of CAP in solvents (0.1N HCL pH 1.2, phosphate buffer pH 6.8, and phosphate buffer pH 7.4) at room temperature with continuous stirring for 24 h [12]. By using the UV double-beam spectrophotometer (Shimadzu 1800), the equilibrium solubility was determined by taking the supernatant liquid and analyzing it at 240 nm.

2.2.1.3 Loss on drying

Loss on drying (LOD) was performed for the determination of loss in weight of compound after drying at a temperature 5^oC to 10^oC below its melting point [20]. The LOD of CAP was performed by taking 1 g (W1) of CAP into a dried, weighed crucible. Then it was dried in an oven at 105°C for 1 h and cooled in a desiccator. The sample was weighed again (W2). The % LOD was calculated by using the following formula (Equation 1) [2].

$$\% \text{ LOD} = W1 - W2 / W1 \times 100 \qquad (1)$$

2.2.1.4 Method development

We had developed a rapid, simple, accurate, economical [22] and precise UV spectrophotometric method using UV double beam spectrophotometer (Shimadzu 1800) for the estimation of CAP in its tablet dosage form. The absorbance maxima selected at 240 nm. Water was used as a solvent which was the commercially available universal solvent. The linearity was found to be 5-25 µg/mL with the correlation coefficient (R^2) of 0.9998 [23]. The developed method was validated as per the ICH guidelines [24]. The precision and accuracy was performed. The % RSD was found to be 1.8 % and percent recovery was found in the range of 98.16 - 105.1% respectively [25]. The assay of the available tablet formulation of CAP was carried out by applying the developed UV spectrophotometric method and it was found 99.374%. Finally we had applied the developed and validated UV spectrophotometric method for the determination of the drug release of the formulated modified release tablets of CAP.

2.2.1.5 Quantification of CAP by UV spectroscopy

For the quantitative determination, the stock solutions of CAP (100 µg/mL) were prepared in 0.1N HCL pH 1.2, phosphate buffer pH 6.8, and phosphate buffer pH 7.4. This were then analysed using a UV double- beam spectrophotometer (Shimadzu 1800) in the range of 200-400 nm for the determination of λ_{max}. The standard solutions in the range of 5-25 µg/mL were prepared from the above stock solution. Each standard solution was then analysed spectrophotometrically and the absorbance was recorded at the λ_{max} obtained. The calibration curves were plotted using the obtained absorbance-concentration data. All the calibration curves were found to be linear in the concentration range of 5-25 µg/mL. The coefficient of regression values R^2 = 0.9983, R^2 = 0.972 and R^2 = 0.9614 and slope y = 0.0316x+0.114, y = 0.0341x+0.0783 and y = 0.0288x+0.0417 for 0.1N HCL pH 1.2, phosphate buffer pH 6.8 and phosphate buffer pH 7.4 respectively.

2.2.1.6 Fourier transform infrared spectroscopy

The FTIR spectra's of CAP, HPC, SA, Lactose and Magnesium stearate were obtained using FTIR (BRUKER OPTICS). The 4000 - 400 cm^{-1} frequency range was used for the scanning of the spectrum of the drug as well as all other excipients [26]. The spectra's obtained were shows various peaks. These spectra's were then compared with the standard spectra's of the drug and excipients for the identification of corresponding functional groups present in the structure of the drug CAP and excipients [27, 28].

2.2.1.7 Differential scanning calorimetry

The DSC thermogram of CAP was obtained by using DSC (PERKIN DSC 600). The sample 2-5mg was taken for the analysis and sealed it in aluminium pans [14]. The sample was heated in sealed aluminium pans [29] over a temperature range of 30-150°C with nitrogen flow rate of 10°C/min [28, 30].

2.2.1.8 Powder X-ray diffractometry

The powder characteristics of the drug was studied by using powder X-ray diffraction technique (P-XRD) [14, 28]. Bruker AXS D8 Advance (Karlsruhe, Germany) instrument was used to study diffraction patterns of CAP.

2.2.1.9 Drug-excipients compatibility studies

The interactions between the drug and excipients as well as the stability of CAP in presence of various excipients used in the formulation were studied by using the FTIR technique [14]. The FTIR spectrums of CAP, CAP:HPC, CAP:SA, CAP:Lactose, CAP:Mg stearate, physical mixture of CAP:HPC:SA:Lactose:Mg stearate in 1:1 proportion was recorded using FTIR (BRUKER

OPTICS). Also the FTIR spectrum of granules which was prepared by using CAP:HPC:SA:Lactose:IPA:Mg stearate was also recorded [31, 32]. Before taking these FTIR spectrum of all above samples were stored for period of 15 days at the temperature of 40°C ± 2°C and relative humidity 75 % ± 5%. During the storage period all the samples were regularly observed physically for caking, liquification, discolouration and odour or gas formation [33].

The DSC was another technique used for the drug- excipients compatibility study. The DSC analysis was performed using a DSC (PERKIN DSC 600) by the same method which was mentioned as above. It was also used to check interaction of CAP with excipients. Physical mixture of CAP: HPC: SA: Lactose: Mg stearate (1:1:1:1:1) proportion was used for the analysis. DSC thermogram of CAP was compared with the DSC thermogram of the physical mixture of CAP and excipients to study the any possible interaction between the drug and excipients.

2.2.2 Development of modified release tablets

2.2.2.1 Formulation of Preliminary Batches

Preliminary batches were formulated using HPC 15% to 30% [13] and SA 21% to 30% (Table 1). These batches were developed for the selection of proper concentration range of polymers which were then utilized during the construction of factorial design.

Table 1. Composition of preliminary batches.

Ingredients (mg)	F1	F2	F3	F4
Capecitabine	300	300	300	300
HPC	15%	20%	25%	30%
SA	21%	23%	25%	30%
Lactose	q.s	q.s	q.s	q.s
IPA	q.s	q.s	q.s	q.s
Mg stearate	2	2	2	2
Total	700	700	700	700

2.2.2.2 Factorial design

Preliminary studies were carried out for the selection of the concentrations range of both the polymers before applying the experimental design. After the development of preliminary batches, 3^2 full factorial design was used in which the amounts of HPC (X_1) and SA (X_2) were selected as independent variables to study its effect on dependent variables i.e. in-vitro drug release and swelling index. All other formulation and processing parameters were kept constant during the study [14, 34].

2.2.2.3 Formulation of tablets

All the ingredients were accurately weighed and individually passed through a mesh # 60 sieve [35]. For the proper mixing of all the ingredients, CAP, HPC and SA were mixed thoroughly on a butter paper with the help of spatula for 30 min. Then lactose was blended in the above mixture in a mortar and pestle for 10 min [14]. Further IPA was used as a non-aqueous granulating liquid for the preparation of a damp mass [36]. To prepare the granules this damp mass was then passed through mesh # 18 sieve [37]. Granules were dried at 60°C [38] and the dried granules were again passed through mesh # 12 sieve to obtained the uniform size granules. Finally, Mg stearate was added and mixed properly for 1-2 min [32]. The granules were then compressed on a rotary tablet compression machine (JAGUAR JMD-4-8) to obtain a final tablet weight of 700 mg by using 12 mm flat punches [37]. Similarly nine formulations (Table 2) were prepared.

Table 2. Composition of the formulation batches containing different concentration of polymers

Ingredients (mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Capecitabine	300	300	300	300	300	300	300	300	300
HPC	120	150	180	120	150	180	120	150	180
SA	126	126	126	138	138	138	150	150	150
Lactose	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
IPA	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Mg stearate	2	2	2	2	2	2	2	2	2
Total	700	700	700	700	700	700	700	700	700

2.2.3 Evaluation of granules

The prepared granules were evaluated for compressibility or Carr's index and angle of repose to study the flow properties of granules [10, 39].

2.2.4 Evaluation of tablets.

2.2.4.1 Thickness

Randomly selected three tablets from each formulation batch, were evaluated for thickness with the help of Vernier Calliper (AEROSPACE) and there average and standard deviation values were calculated [40, 41].

2.2.4.2 Hardness

The three tablets from each batch were randomly selected, and measure their hardness using a Monsanto Hardness Tester then the mean and standard deviation value were calculated [42]. Hardness is measured in terms of kg/cm^2 [43, 44].

2.2.4.3 Friability

The tablet friability was determined using Roche's friabilator [10] (ELECTROLABEF2W ver.1.45). Ten tablets were selected from each formulation batch and weighed the tablet sample (W). The tablets were then placed in the drum and the drum was rotated at 25 rpm (100 revolutions) for 4 min. After the completion of test, the tablets were removed from the drum, de-dusted and weighed again (W_0) [20, 41, 44]. Maximum mean weight loss of not more than 1% is acceptable [9, 10]. The test was carried out in triplicate and the average value was calculated. Friability was calculated by using equation 2

$$f = (W - W_0 / W) \times 100 \qquad (2)$$

2.2.4.4 Weight variation

Weight variation test was carried out by the random selection of 20 tablets from each batch [45]. These tablets were then weighed individually using the digital electronic balance (SHIMADZU AUX 220). The average weight was calculated and compared with the individual weight [38].

2.2.4.5 Content uniformity

Drug content uniformity was studied by randomly selecting three tablets from each batch. The tablets were crushed and homogenized in a glass mortar to form a powder [46]. From this powder amount equivalent to 10 mg of CAP was accurately weighed and dissolved in 100 mL of phosphate buffer pH 6.8 to make a stock solution of 100 µg/mL. This solution was then sonicated for 30 min and then filtered through a whatman filter paper to obtain clear solution. The 1 mL sample was withdrawn from this stock solution and diluted up to 10 mL in a volumetric flask. The drug concentration was determined at 236.8 nm by using the UV spectroscopic method as depicted above [10, 20, 47] .

2.2.4.6 Swelling index

To study the swelling behaviour of tablets, a piece of plastic paper folded twice was placed in a small petri dish containing medium used for study [14, 32]. Three randomly selected tablets were weighed individually (W_1). These tablets were then kept on a paper in the petri dish and immersed it separately in a petri dishes containing 45mL of 0.1 N HCL for 2 h, phosphate buffer pH 6.8 for next 5 h and then phosphate buffer pH 7.4 for up to 12 h [44,48]. After the specific time interval the tablets were removed from the petri dishes, and the excess surface water present was removed carefully with the help of tissue paper. Then these swollen tablets were reweighed again and the weight was recorded as final weight (W_2). The study was carried out in triplicates % swelling index was calculated by using the following equation 3 [14, 49, 50]

$$\text{Swelling index} = (W_2 - W_1 / W_2) \times 100 \qquad (3)$$

Where, W_1 = initial weight of tablet

W_2 = weight of tablet after 12 h.

2.2.4.7 In - vitro drug release study

The *in-vitro* drug release study was carried out using the United States Pharmacopoeia (USP) - type II dissolution apparatus (ELECTROLAB TDT - 08-L) [32,34]. The dissolution medium 900 mL of 0.1 N HCL pH 1.2, phosphate buffer pH 6.8, and phosphate buffer pH 7.4 were used to simulate the GIT conditions [51]. The study was carried out at $37^{o}C \pm 0.5^{o}C$ with a paddle rotation speed of about 50 rpm [52]. The tablets were firstly placed in 900 mL of 0.1 N HCL of pH 1.2 for 2 h because the average gastric emptying time is 1-2 h. Then the dissolution medium was replaced with 900 ml of phosphate buffer pH 6.8 for next 5 h as the average small intestinal transit time is 3-6 h. After that at last the dissolution medium was replaced with 900 mL of phosphate buffer pH 7.4 and the drug release study was carried out for 24 h [4,11,51,53]. The 1 mL sample was withdrawn after each 1 h and filtered through whatman filter paper and diluted up to 10 mL with the same solvent [54]. The sink conditions were maintained with the addition of equal volume of fresh dissolution medium. The samples were then analysed by using the UV double-beam spectrophotometer (Shimadzu 1800) at 239.6 nm, 238.6 nm, and 239.2 nm for 0.1 N HCL of pH 1.2, phosphate buffer pH 6.8, and phosphate buffer pH 7.4 respectively.

2.2.4.8 Kinetic data treatment

The obtained drug release data were analysed with the different mathematical models to study the mechanism of drug release patterns from the developed tablets. Different kinetic models used for this study include First-order kinetic, Zero-order kinetic, Higuchi equation, Hixson-Crowell equation and Korsmeyer-Peppas equation [29, 55].

2.2.4.9 Stability studies of optimized formulation

Three months of short term stability study was carried out for the optimized tablet formulation of modified release tablets of CAP. For the stability studies, the tablets were firstly wrapped in the aluminium foil and then placed in a stability chamber kept at accelerated conditions of temperature 40^{o}C ± 2°C and relative humidity of about 75% ± 5%. Tablets were removed from stability chamber after completion of three months and evaluated for appearance, drug content and *in vitro* drug release study [14, 30, 56].

3. Results and discussions

3.1 Preformulation study

3.1.1 Characterization of pure drug

The FTIR spectra of pure CAP (Figure 1), which exhibited various peaks at wave numbers in cm^{1}, which is similar to the functional groups present in the structure of CAP [27,57]. The FTIR spectrum of CAP showed various characteristic signals. The purity of a CAP was confirmed by the presence of absorption bands corresponding to the functional groups present in the structure of CAP and also due to the absence of any other uncountable peaks [4,58].

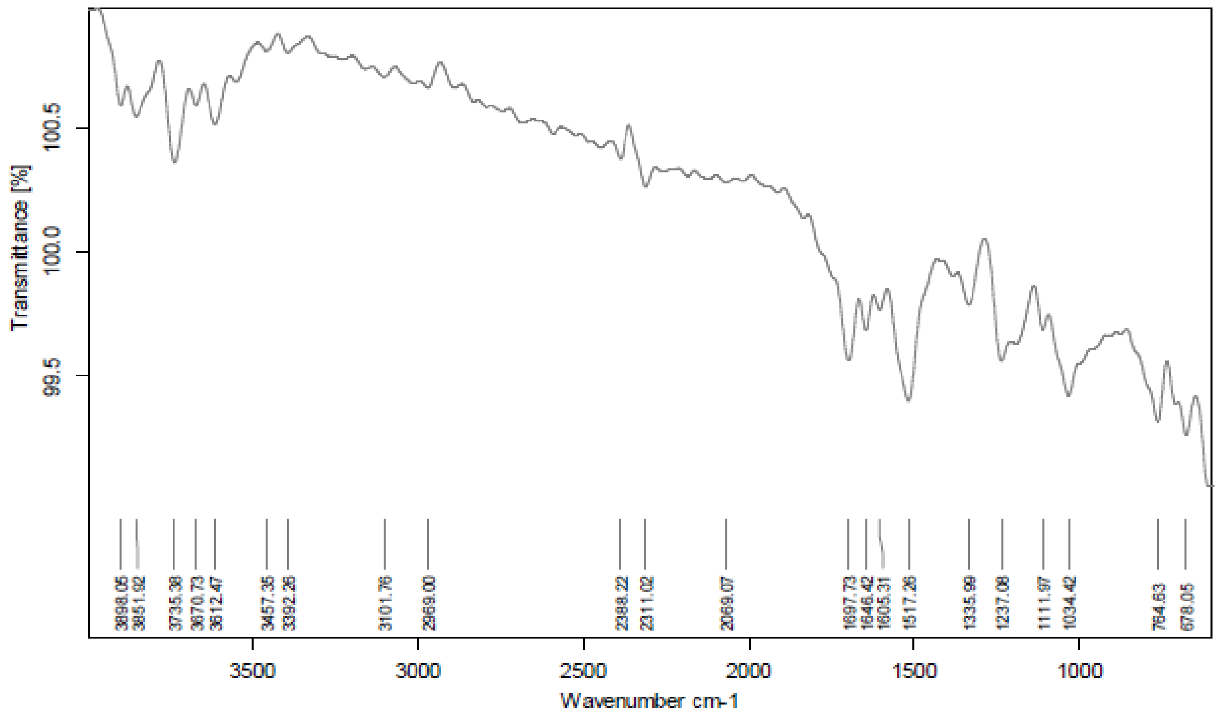


Figure 1. FTIR spectrum of CAP.

The DSC thermogram of pure CAP (Figure 2) showed sharp endothermic peak at 124.16^{o}C corresponding to its melting point [4] and it was also indicates crystalline nature of compound. Results of melting point, solubility and loss on drying of CAP was reported in table 3.

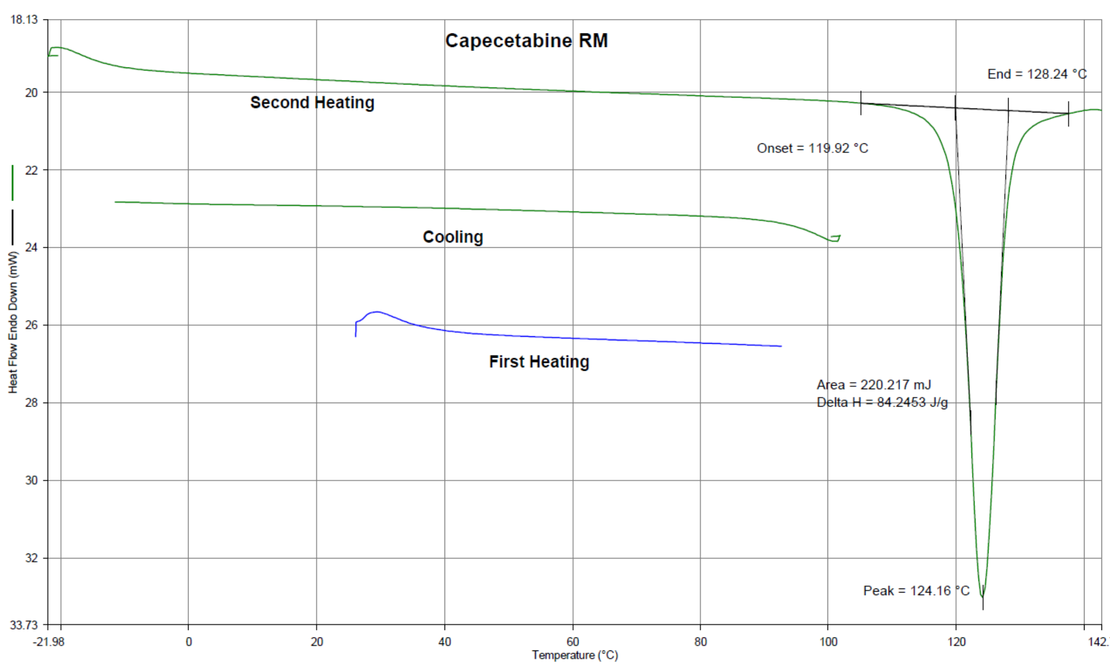


Figure 2. DSC thermogram of CAP.

X-ray diffractometer was used to study the diffraction pattern of pure CAP. The major characteristics diffraction peaks of CAP at a diffraction angle of 2θ at 10.4199º, 19.6453º, 19.9336º, 25.1806º, 28.2077º, 36.0781º and 40.0277º with peak intensities of 1076, 1658, 4077, 1114, 743,562 and 561 respectively (Figure 3). The P-XRD pattern of CAP gives very sharp and intense peaks which was also confirmed the crystallinity of the compound [38].

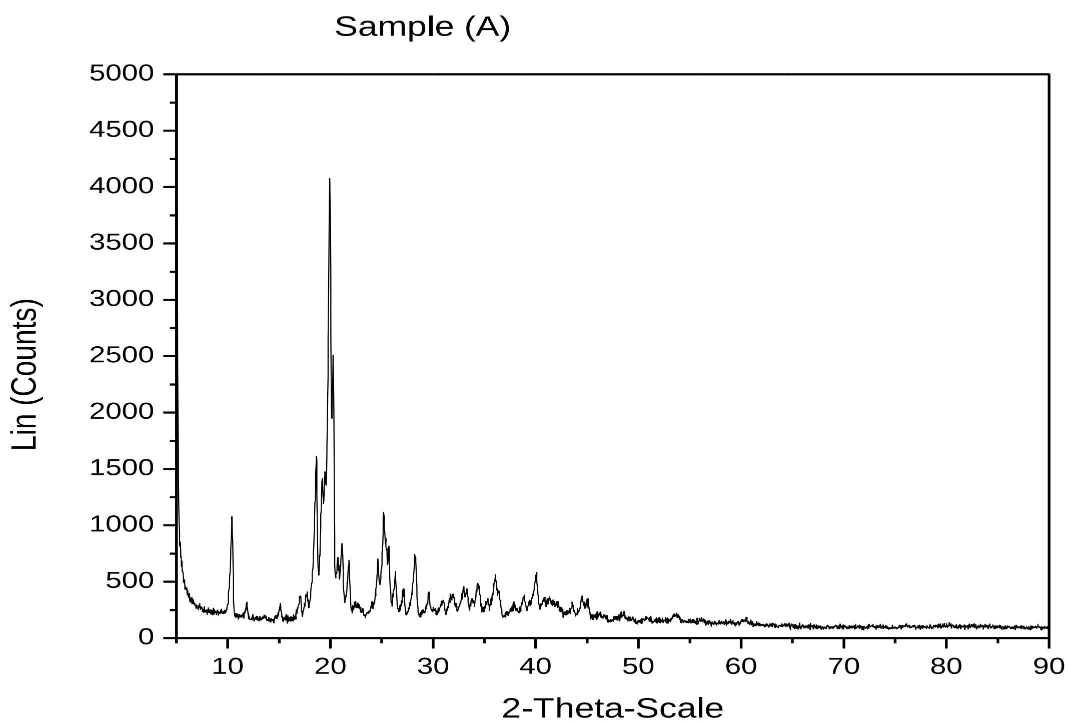


Figure 3. P-XRD of CAP

3.1.2 Drug- excipients compatibility studies

FTIR studies were carried out for CAP, CAP and polymer mixture, CAP and excipients mixture, and also granules prepared by using CAP and all this polymers and excipients with the addition of IPA as granulating liquid. The recorded FTIR spectrums (Figure 4 [I]) A-F, of the spectrum shows the presence of principal peaks of CAP which was indicates that there was no interaction between CAP, polymers and excipients [59]. Therefore it was confirmed the absence of incompatibilities between CAP, polymers and excipients which was supported by the overlaid FTIR spectrum "F" (Figure 4 [I]).

The DSC study was carried out for pure CAP, CAP with physical mixture of polymers and excipients. The DSC thermogram (Figure 4 [II]) of CAP shows sharp endothermic peak at 124.16°C which was also present in the physical mixture of drug, polymer and excipients at 118.35°C. No major changes are found between these peak values which indicated that there was no any incompatibility found between CAP, polymers and excipients.

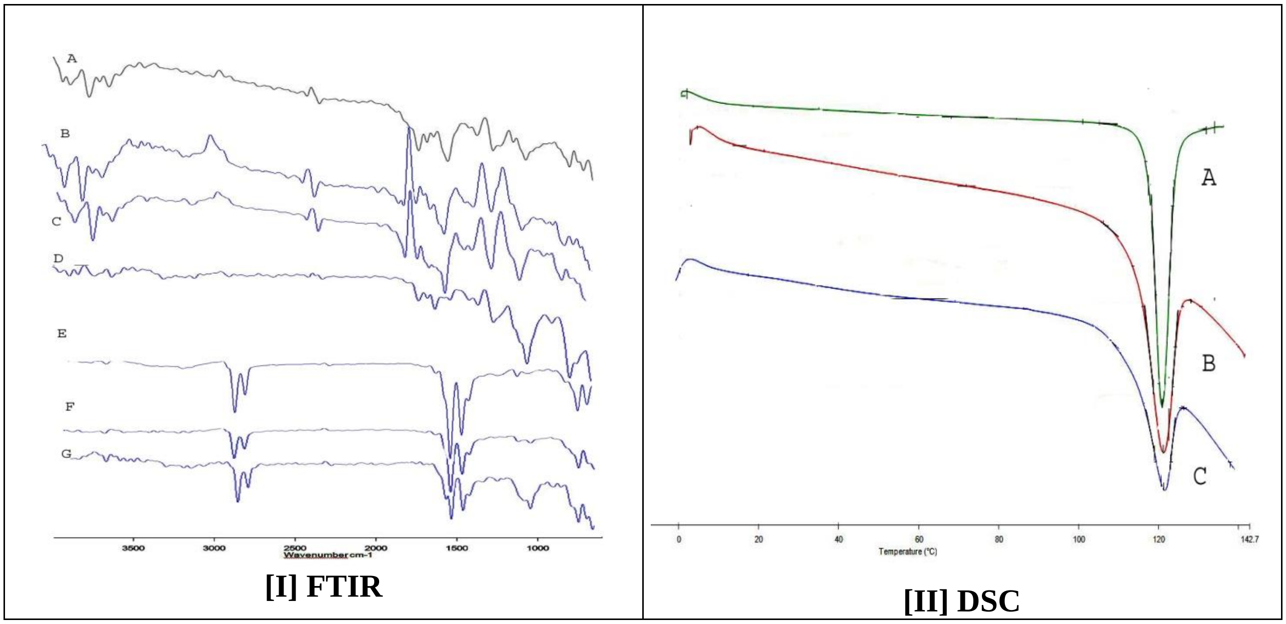


Figure 4. Drug polymer / excipient compatibility studies by FTIR and DSC.

Table 3. Results of melting point, solubility and loss on drying of CAP.

Test	Observed result
Melting point (°C)(Alison,2014;O'Neil et al., 2001)	115-120 °C
Solubility (mg/mL)(Alison,2014;O'Neil et al., 2001 Moffat et al., 2004)	
1. Water	29.35 mg/ mL
2. 0.1 N HCL pH 1.2	65.24 mg/mL
3. Phosphate buffer pH 6.8	79.37 mg/mL
4. Phosphate buffer pH 7.4	88.72 mg/mL
% Loss on drying (LOD)	0.39 %

3.2 Evaluation of granules

The observation of angle of repose and Carr's index studies for all nine formulation were found in the range 32-34°and 11-14% respectively [39]. From these results it was concluded that all the formulation had good flow properties which required during compression of the tablets.

3.3 Characterization of tablets of CAP

3.3.1. In process quality control test

The formulated tablets were evaluated for the physical characterization like thickness, hardness or crushing strength, friability, average weight, and uniformity of drug content (Table 4). For all the formulations thickness was found to be in the range of 4.1-4.26 mm with the average of 4.12 mm. The hardness of the tablets was found to be between 11.5 - 12.36 kg/cm^2, with the average of 11.97 kg/cm^2 it was complies with the standard values reported in literature. The minimum hardness required for the tablet production is 4 kg/cm^2 [9]. The average weight of tablets of all formulation were lies in the range between 687.5 mg to 702.5 mg. Therefore all the nine formulations passed the weight variation test as per USP [20].

For all the nine formulations percent drug content was found to between 91.03% and 109.32%. Hence, all the tablets were complied with IP 2010 standards (CAP tablet contains not less than 90% and not more than 110% of the stated amount of CAP) [27].

Table 4. Results of quality control tests of formulated modified release tablets of CAP.

Batch code	**Thickness (mm)***	**Hardness (kg/cm^2)***	**Friability (%)**	**Weight (mg)****	**Drug content (%)*****
F1	4.1 ± 0.1	11.5 ± 0.5	0.20 ± 0.0057	696.52	105.88 ± 1.27
F2	4.12 ± 0.02	11.83 ± 0.76	0.00 ± 0.00	693.95	109.32 ± 0.99
F3	4.03 ± 0.05	12.16 ± 0.28	0.20 ±0.0057	692.5	102.4 ± 1.70
F4	4.26 ± 0.057	11.43 ± 0.25	0.23 ± 0.057	693.07	94.85 ± 0.66
F5	4.1 ± 0	12 ± 0.5	0.32 ± 0.02	694.00	102.56 ± 1.20
F6	4.13 ± 0.0057	12.36 ± 0.15	0.53 ± 0.057	687.5	104.73 ± 0.37
F7	4.08 ± 0.0057	12.1 ± 0.52	0.22 ± 0.020	702.5	105.17 ± 0.24
F8	4.2 ± 0	12.13 ± 0.55	0.21 ± 0.023	700.3	98.32 ± 0.59
F9	4.10 ± 0.01	12.26 ± 0.15	0.22 ± 0.025	699.25	91.03 ± 0.16

*Mean (± SD) of three independent determinations.
**Average weight of 20 tablets.

***Mean (± SD) three tablets.

3.3.2 Swelling index

Swelling index is an important parameter when we used the polymers in the development of a formulation. The extent of swelling was measured as % weight gain by the tablet. It was proportional to the degree of hydration of the polymers. The HPC and SA both are hydrophilic polymers [60], therefore in present study it was found that the concentration as well as ratio of both of these polymers plays a very important role in the swelling behaviour of modified release tablets of CAP. The highest degree of swelling was obtained from batch F9. It shows 39.90 % swelling in 0.1 N HCL pH 1.2 after 2 h; and 92.94% swelling in phosphate buffer pH 7.4 after 12 h (Table 5), which is composed of HPC and SA, having 180 mg and 150 mg respectively. The lowest degree of swelling was obtained from batch F1, that is 21.44% ± 0.42 in 0.1 N HCL pH 1.2 after 2 h; and 45.23% ± 0.30 in phosphate buffer pH 7.4 after 12 h, which is composed of HPC and SA having 120 mg and 126 mg respectively. These results were indicated that swelling index was increased with increase in concentration of HPC and SA which forms the more compact structure of the hydrated gel layer and slowed down the penetration of fluids [61] .

Table 5. Results of swelling index in 0.1 N HCL pH 1.2 and phosphate buffer pH 7.4.

Batch code	Swelling index (%) in 0.1 N HCL pH 1.2 (2 h)*	Swelling index (%) in phosphate buffer pH 7.4(12 h)*
F1	21.44 ± 0.42	45.23 ± 0.30
F2	23.57 ± 0.31	47.25 ± 0.28
F3	25.59 ± 0.43	62.82 ± 0.09
F4	21.66 ± 0.28	63.7 ± 0.13
F5	30.46 ± 0.16	66.77 ± 0.12
F6	31.72 ± 0.06	78.90 ± 0.29
F7	32.75 ± 0.23	82.57 ± 0.77
F8	38.65 ± 0.10	89.02 ± 0.46
F9	39.90 ± 0.15	92.94 ± 0.08

***Mean (± SD) of three independent determination.**

3.3.3 In- vitro drug release study

The developed modified release tablets of CAP are hydrophilic polymeric matrix systems. In these systems the drug particles are dispersed in a hydrophilic polymeric matrix from which drug release occurs by dissolution of the drug, diffusion through the gel layer, and erosion of the matrix [9]. Percent drug release in 0.1 N HCL pH 1.2 after 2 h, F1- 15.93%, F2- 10.71%, F3- 9.81%, F4- 15.75%, F5- 10.35%, F6- 8.28%, F7- 15.21%, F8- 7.74% and F9- 6.66%. Formulation F3, F6, F8 and F9 shows less than 10% of the drug release after 2 h in 0.1 N HCL pH 1.2 [62]. This was due to the mild gelling properties of alginate which was pH dependent and allows the drug to entrap in the matrix formed by the polymers. At gastric pH, alginate will get shrink and the entrapped drug within the polymer matrix was not released [15]. The SA also shows higher ability of swelling in neutral medium than in acidic medium therefore it gives less drug release in acidic medium [35]. Also HPC was used as an extended release matrix forming agent. Addition of an anionic agent like SA increases the viscosity of HPC and hence decreases the drug release rate by increasing the thickness of diffusional layer [13]. The percent drug release with respect to time shows in Figure 5. The percent drug release in phosphate buffer pH 6.8 and 7.4, for formulations, F1 – 92.73%, F4 – 79.59 % and F7 – 91.35% in 18 h, 18 h and 19 h period respectively. For formulations, F2 – 99.68% , F5 – 94.41% and F8 – 90.32% after 18 h, 20 h and 24 h respectively and formulations F3 – 93.99%, F6 – 96.8 and F9 – 84.51% after 21 h, 23 h and 24 h respectively. The higher erosion in the neutral medium leads to faster drug release than acidic medium [63, 64]. From all these results of drug release study it was found that formulation F8 shows maximum percent drug release 90.32% up to 24 h and only 7.74 % drug release in 0.1 N HCL (pH 1.2) at 2h which was complies with standards reported in literature [62] when compared with the rest of formulations. Therefore formulation F8 was considered as a best formulation depending on its higher drug release characteristics and swelling properties.

Though formulation F9 was released only 6.66% drug in 0.1 N HCL (pH 1.2) in 2h with highest degree of swelling when compared with F8 as well as rest of the formulations but it released only 84.51% of drug within 24 h which was not comply with standards reported in official compendia [27]. This was due to the HPC and SA both were the hydrophilic polymers [13,65] when the tablets containing these polymers comes in contact with water, the polymers will show rapid hydration of the tablet matrix and results in higher degree of swelling of the polymers [66,67]. It forms a diffusion barrier by forming the hydrated viscous gel layer around the tablet surface. This leads resistance to transport of the dissolution medium into the tablet and alternatively transport or the diffusion of the drug from the tablet core to the dissolution medium due to increased thickness of the diffusional layer [68].

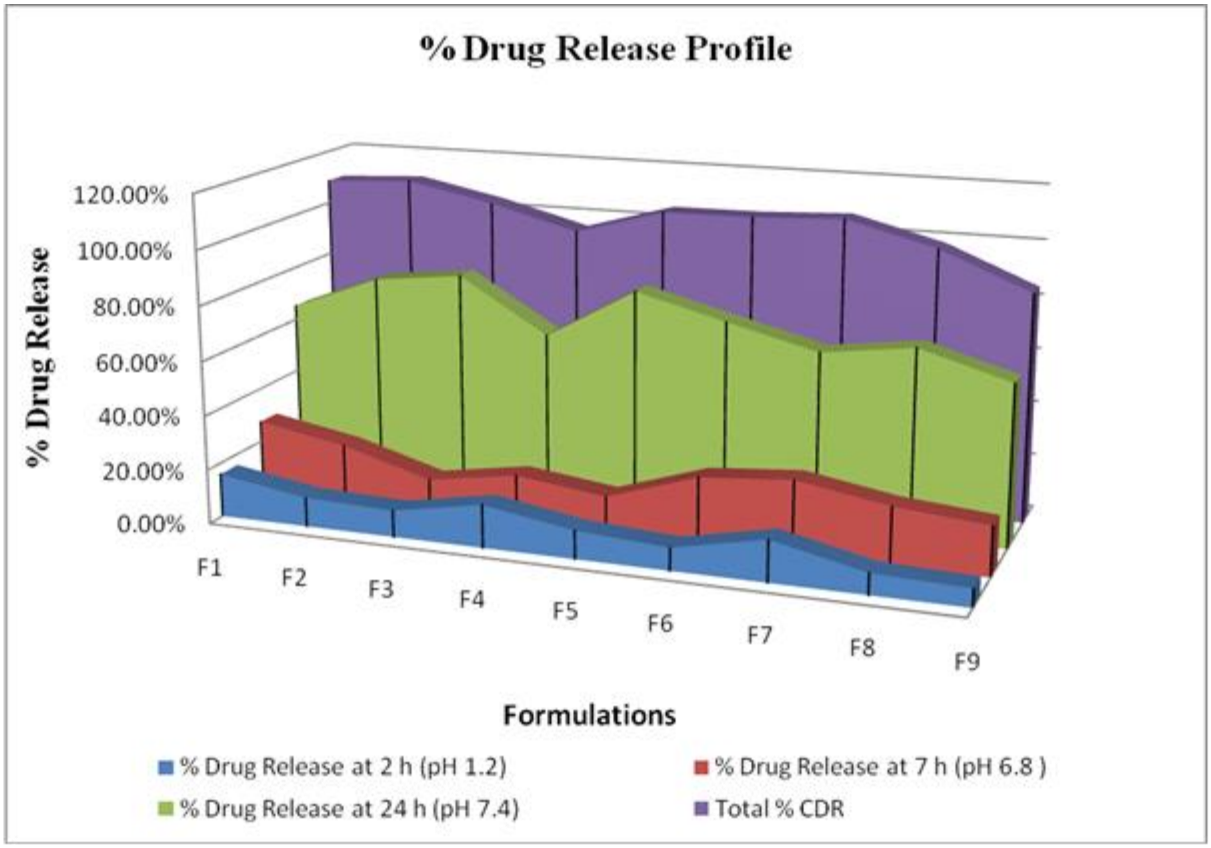


Figure 5. % Drug release of formulation F1 to F9

3.3.4 Kinetic data treatment.

Various mathematical models such as Zero order kinetics, First order kinetics, Higuchi model, Hixson- Crowell model and Korsmeyer-Peppas model were used to study the drug release mechanism from the tablets. The best model to describe the drug release from the tablets was selected on the basis of the coefficient of determination (R^2) value (Table 8). Formulations F1, F4 and F7 followed Korsmeyer-Peppas kinetics [69]. These all formulations contain lowest concentration of HPC (i.e. 20 mg). Therefore these formulations shows least swelling when they were exposed to the dissolution medium and drug release retarded up to 18 h, 18 h and 19 h respectively. The value of "*n*" determines the drug release mechanism from the device, *n* is the diffusional exponent [70].The values of "*n*" were found 0.8101, 0.8292 and 0.8357 for F1, F4 and F7 respectively (Table 6) which indicates that these formulations followed Anomalous transport [69]. In anomalous transport the drug release from the device takes place by diffusion and erosion mechanism in combination [32].

Formulations F2, F5 and F8 also exhibited Korsmeyer - Peppas kinetics. These formulations contains intermediate amount of HPC (i.e. 25 mg). So it shows moderate swelling when exposed to dissolution medium and retarded the drug release up to 18 h, 20 h and 24 h respectively. Except formulations F1, F4 and F7 all remaining formulations showed the values of "*n*" in the range between 1.0338- 1.1127. Therefore these all formulations followed super case-II transport it indicates that the release of the drug was erosion controlled [71].

The remaining three formulations F3, F6 and F9 exhibited zero order kinetics. These all formulations contain maximum concentration of HPC (i.e. 30 mg). Therefore these formulations showed maximum swelling when it comes in contact with the dissolution medium [14]. The diffusion of drug takes place through the swelled polymeric matrix. These dosage forms releases the drug slowly and retarded the drug release up to 21 h, 23 h and 24 h respectively.

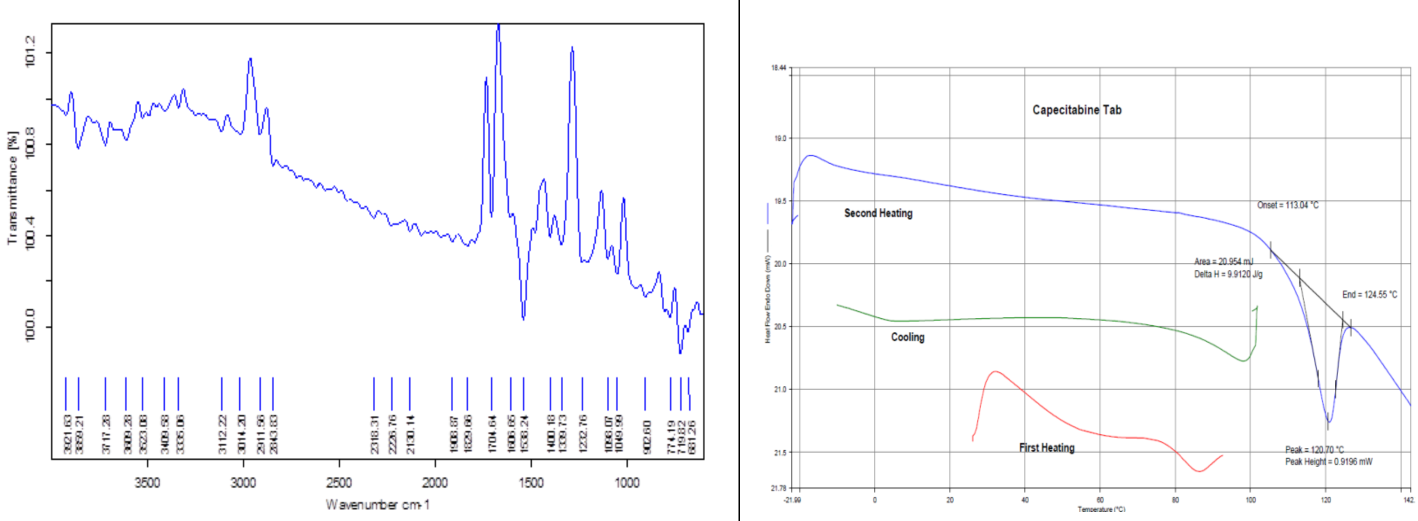
Table 6. Kinetic release studies of formulations.

Batch code	**Zero order**		**First order**		**Higuchi**		**Korsmeyer-Peppas**		**Hixson-Crowell**	
	R^2	K_0	R^2	K_1	R^2	K_H	R^2	n	R^2	K_S
F1	0.9738	6.0366	0.859	0.2605	0.9778	25.50	0.9792	0.8101	0.7353	-0.2651
F2	0.9653	6.1305	0.8913	0.2613	0.9485	26.00	0.9811	1.0606	0.6833	-0.2664
F3	0.962	4.9428	0.9564	0.2211	0.9012	22.65	0.9465	1.0338	0.8868	-0.2237
F4	0.9828	5.2966	0.9321	0.2532	0.9778	22.47	0.9914	0.8292	0.7746	-0.2537
F5	0.9328	5.238	0.9543	0.2326	0.8645	23.42	0.9646	1.0256	0.2921	-0.2357
F6	0.9783	4.5686	0.8427	0.2024	0.9671	21.91	0.9736	1.07	0.9504	-0.2051
F7	0.962	5.6084	0.8615	0.2457	0.9734	24.44	0.9814	0.8357	0.9126	-0.2495
F8	0.9752	4.0858	0.8453	0.1911	0.9657	20.01	0.9866	1.0447	0.8594	-0.1921
F9	0.9852	3.6745	0.827	0.1866	0.9723	18.00	0.9648	1.1127	0.8335	-0.1854

R^2: Correlation coefficient of different models
K_0: Zero order release rate constant
K_1: First order release rate constant
K_H: Higuchi release rate constant
K_S: Hixson-Crowell release rate constant
n: Drug release exponent

3.4 Evaluation of optimized formulation

The FTIR spectrum (Figure 6[A]) of optimized formulation tablet (OFT) of CAP shows various characteristics signal. The peaks shown by the OFT are similar to that present in the structure of CAP. The presence of absorption bands similar to the functional groups that are present in the structure of CAP , as well as the absence of any other uncountable peaks in the FTIR spectrum of OFT gives the confirmation of the purity of formulation [4,27].



(A) **(B)**

Figure 6. [A]- FTIR spectrum of OFT, [B]-DSC thermogram of OFT

The DSC thermogram of OFT (Figure 6[B]) showed a sharp endothermic peak at 120.70^{o}C corresponding to the melting point of CAP which was near about similar to the DSC thermogram of pure CAP which shows sharp endothermic peak at 124.16^{o}C [4,44]. These results indicated that the crystalline nature of the CAP was remained unchanged after the compression of the tablets. From this thermogram it was also confirmed that there was no any polymorphic change in the CAP after compression of the tablets.

The P-XRD pattern of CAP gives major characteristics diffraction peaks at a diffraction angle of 2θ at 10.4199º, 19.6453º, 19.9336º, 25.1806º, 28.2077º, 36.0781º and 40.0277º with peak intensities of 1076, 1658, 4077, 1114, 743,562 and 561 respectively (Figure 3). The OFT shows the major diffraction peak at an diffraction angle of 2θ at 12.265º, 16.1858º, 19.5588º, 19.7895º, 21.003º, 23.5661º, 25.3536º and 37.3754º with the peak intensities of about 1046, 974, 1320, 3055, 1125, 756, 518 and 446 respectively (Figure 7). In the same manner compressed tablet (CT) of HPC, SA and lactose showed the diffraction at a diffraction angle of 2θ at 12.2074, 16.157, 19.53, 19.6742, 20.9427, 23.5058, 25.3247 and 37.2889 with peak intensities of 1428, 1633, 2171, 4680, 1658, 781, 704 and 574 respectively (Figure 7). These results were indicated that there was no major changes in the diffraction peaks of OFT and CT of HPC, SA and lactose. It was also showed that there was decrease in the intensity of peaks of CAP because of total concentration of CAP in the OFT prepared by non-aqueous wet granulation method. From these results it was clear that there was formation of drug polymer matrix. More diffraction peaks were generated which was indication for the physical mixture of CAP with polymer. These P-XRD studies were also confirmed that CAP was crystalline compound and its crystallinity remain unchanged after the compression of tablets means there was no effect of compression on the crystalline nature of the compound [38]. This was due to the presence of sharp and intense diffraction peaks of CAP in OFT [14].

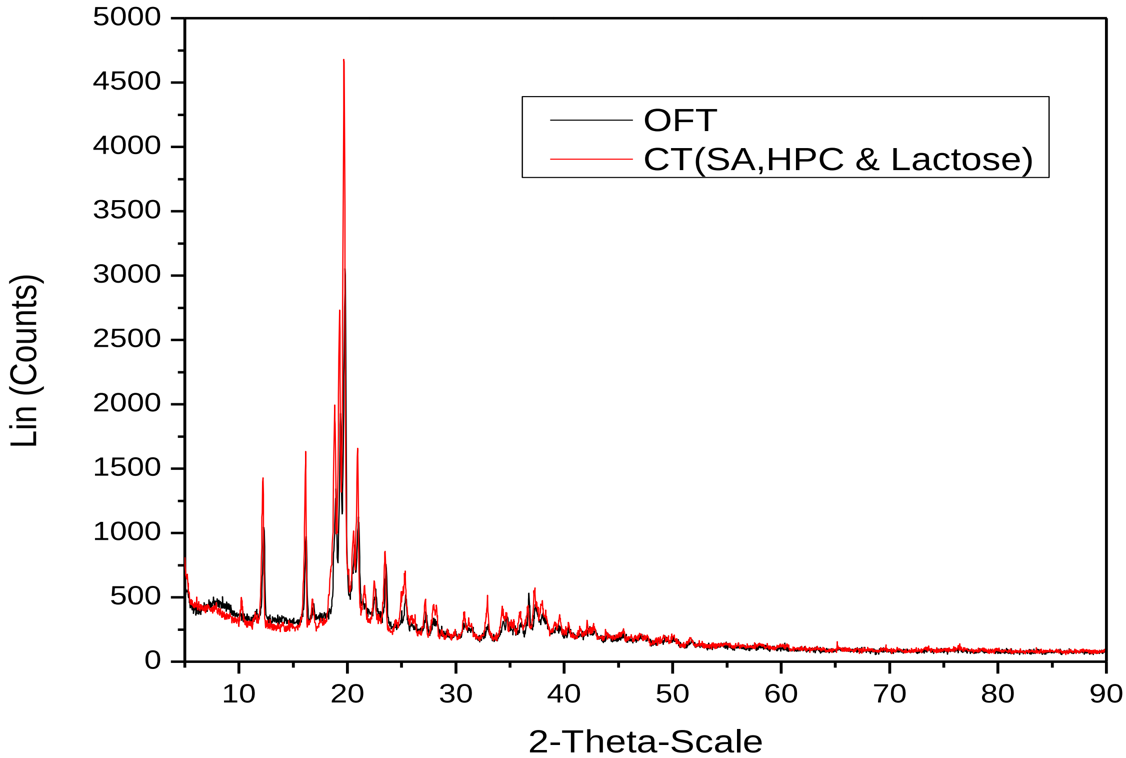


Figure 7. P-XRD overlay of OFT and CT (SA, HPC and Lactose)

3.5 Short term stability studies

The OFT of CAP was evaluated after 3 months of storage period. The tablets were evaluated for physical appearance, drug content and % drug release study. From the results (Table 7) it was shown that there were no visible changes in the appearance of the modified release tablets of CAP at the end of 3 months storage period. Also there was no difference in drug content and % drug release, which indicates that F8 was stable.

Table 7. Results of stability studies of CAP modified release tablet (OFT).

Sr. No	Parameters	Observations	
		Before stability study	After stability study
1.	Physical appearance	White	White
2.	Drug content (%)	98.32%	97.15%
3.	Drug release (%)	98.06%	97.23%

4. Conclusion

We had successfully developed the modified release tablet formulations of CAP. Formulation F8 exhibited extended drug release up to 24 h with the maximum swelling characteristics. It was also shows negligible amount of the % drug releases (below 10%) in the gastric environment of the stomach without coating of gastric resistant or enteric coating polymers was achieved. Here we successfully utilize the shrinking ability of SA due this the drug is not released at low pH of the gastric environment. Combination of HPC as an extended release matrix former with SA as a sustained release agent and also have mild gelling properties shows better retardation of drug release characteristics. The drug release was retarded which was depends on formation of hydrated viscous layer around the tablet matrix due to the swelling and gelling properties of hydrophilic polymers that is HPC and SA. The CAP was the crystalline compound, from the DSC and P-XRD studies it was concluded that the crystallinity of CAP was remained unchanged after the compression in OFT. Therefore F8 was selected as optimized formulation. The objective of the present research work i.e development of cost effective modified release tablet formation without utilizing enteric coating polymer and coating technology was successfully achieved.

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