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DISSOLUTION KINETICS OF IMMEDIATE RELEASE MINI-TABLETS OF CEFUROXIME AXETIL

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ABSTRACT

The underlying principle of this research is to design the formulation and characterization of in vitro drug release of an immediate release mini-tablets of cefuroxime axetil. In order to get improved solubility and dissolution rate of cefuroxime axetil in gastrointestinal fluid, the hydrophilic grade of Gelucire 50/13, Poloxamer 188 and Sylysia 350 were used as release modifiers. Initially ten formulations (F1-F10) were prepared by direct compression technique and evaluated the physicochemical properties, in vitro dissolution study and their drug release kinetics parameters. The X-RD pattern specifies its amorphous nature, while Gelucire-50/13 exhibits a semi-crystalline nature. Gelucire 50/13, Poloxamer 188 and Sylysia 350 were typically applicable for the preparation of fast-release formulations. Sylysia 350 based formulation is found to be efficient and its mini-tablets were appropriate for immediate release as compared to Gelucire 50/13 and Poloxamer 188 formulations because of faster drug release that is 100% within 5 min for formulation (F4). There is no considerable alteration in dissolution data on storage at 40°C and 75% relative humidity for three months.

KEYWORDS: Sylysia 350, Gelucire 50/13, Poloxamer 188, Immediate Release, Dissolution efficiency, Mean dissolution time

INTRODUCTION

Mini-tablets have enabled ease of administration during the last century, and popularly filled into capsules or sachets and (or) compressed into larger tablets. They are flat or slightly curved tablets (diameter ranges from 1.0 to 3.0 mm)[1,2] and need to deliver and maintain

desired drug therapy concentration at the specific site. Nevertheless, worldwide surveys have recognized the poor efficacy of conventional dosage forms due to wide range of drug concentration fluctuations in the blood stream.[3] Although these conventional formulations have been replaced by advanced drug delivery systems; ease of administration, degree of efficacy and site specific release still impact the quality of treatment therapy. At the same time, mini tablets offer greater advantages over single unit dosage forms. Many mini-units (mini tablets or tiny pellets) can be pocketed into a capsule or compressed into tablets to prepare multiple unit dosage forms. Upon disintegration, these mini-depots are dispersed and distributed throughout the GI tract. The dose of the multiple unit dosage form is equally divided into a number of subunits (each subunit carry single unit dose). The dose hence is the sum of drug content in each subunit and the functionality of the entire dose is directly correlated to the functionality of the individual subunits. As each subunit of a act as self-contained depots, the multiple dose tablets may thus be divided before ingestion to provide a single unit dose without loss of depot effect and offer controlled release of the drug. The term controlled release consist of both single and multiple unit dosage forms.[4] Benefits of mini tablets for intensive patient care are numerous, such as dose accuracy, increased efficiency, decreased Inter and intra subject variability, no or minimal toxic effects of potent drug overdose, circumvent dose dumping and local irritation. Alternately, drugs which are readily absorbed in small intestine are suitable for mini tablets preparation as they can easily pass through the duodenum exempting gastric emptying and intestinal motility. The developing mini-matrices are a promising area in pharmaceutical research concerned with a high control over the release rate of the drug combined with a high flexibility on the adjustment of both the dose and the release of a drug or drugs and has attracted some attention in the 1990s. Developments of mini-matrices production using tableting strategies became popular alternative to the production of pellets, as they lack solvents (e.g., water) and produce significantly high production yields like the ones observed in extrusion and spheronization. Furthermore, it facilitates defined size and strength with minimal variability within and between batches due to the unique manufacturing process.[5,6] The necessary part of this endeavor is concerned with pharmaceutical compositions containing the 1-acetoxyethyl ester of cefuroxime, which has the approved name cefuroxime axetil, which is formulated in the form of immediate release mini tablets for oral delivery. However, cefuroxime axetil has an extremely low aqueous solubility and poor bioavailability.[7,8] Therefore, initially solid dispersion technology employed for the improvement of bioavailability and therapeutic activity of hydrophobic agent such as cefuroxime axetil due to simplicity of preparation, ease

of optimization and reproducibility.[9,10] The main objectives of this research work was to improve the solubility and dissolution rate of cefuroxime axetil using Gelucire 50/13, Poloxamer 188 and Sylysia 350 as release modifiers.

MATERIALS AND METHODS

Cefuroxime axetil was received as a gift sample from Rachem Pharmaceuticals Ltd (Hyderabad, India). Gelucire 50/13, Poloxamer 188 and Sylysia 350 are the gift sample from Fuji Sylysia (Japan). All other chemicals and solvents were of reagent grade and used without further purification.

Preparation of Cefuroxime axetil solid dispersions using Gelucire 50/13 and Poloxamer 188 along with Neusilin US2 by hot melt granulation

Solid dispersions was prepared by hot melt granulation. Required quantity of CA was added into the melt of Gelucire 50/13/ Poloxamer 188, maintaining a temperature of 60^0 C to obtain a clear molten mixture. Neusilin US2 was preheated to 80^0C in the china disc for 15 mins with mixing. The molten mixture was then added drop-wise over a period of one minute to Neusilin US2 with continued mixing. Hot-melt granulation was performed with proper mixing for 15 minutes to obtain the ternary dispersion granules of drug, Gelucire 50/13 or Poloxamer 188 and Neusilin US2. The dispersion granules were allowed to cool to room temperature by air-cooling followed by sieving through mesh #18 BSS.[11] The results of immediate release formulation are shown in table 1.

Table 1: Immediate release formulation using solid dispersions of CA & Sylysia 350, CA & Poloxamer 188, and CA & Gelucire 50/13.

Immediate Release Formulation using Solid dispersion of CA & Sylysia 350										
Formulations	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
SD of CA & Sylysia 350	120	120	120	120	120	120	120	120	120	120
MCC 102	20	17.6	16.4	15.2	14	12.8	11.6	10.4	9.2	8
CP	0	2.4 (2%CP)	3.6 (3%CP)	4.8 (4%CP)	6 (5%CP)	7.2 (6%CP)	8.4 (7%CP)	9.6 (8%CP)	10.8 (9%CP)	12 (10%CP)
Immediate Release Formulation using Solid dispersion of CA & Poloxamer 188										
SD of CA & Poloxamer 188	135	135	135	135	135	135	135	135	135	135
MCC 102	20	17.3	15.95	14.6	13.25	11.9	10.55	9.2	7.85	6.5
CP	0	2.7 (2%CP)	4.05 (3%CP)	5.4 (4%CP)	6.75 (5%CP)	8.1 (6%CP)	9.45 (7%CP)	10.8 (8%CP)	12.15 (9%CP)	13.5 (10%CP)
Immediate Release Formulation using Solid dispersion of CA & Gelucire 50/13										
SD of CA & Gelucire 50/13	135	135	135	135	135	135	135	135	135	135
MCC 102	20	17.3	15.95	14.6	13.25	11.9	10.55	9.2	7.85	6.5
CP	0	2.7 (2% CP)	4.05 (3% CP)	5.4 (4% CP)	6.75 (5% CP)	8.1 (6% CP)	9.45 (7% CP)	10. (8% CP)	12.15 (9% CP)	13.5 (10% CP)

Cefuroxime axetil solid dispersions using Sylysia 350 by solvent evaporation method

The solid dispersions of Cefuroxime axetil and Sylysia 350 in various drug-to-carrier weight ratios were prepared by solvent evaporation method. Required amount of sylysia 350 was dissolved in sufficient quantity of acetone in a beaker and Cefuroxime axetil was added and mixed to dissolve. Then the solvent was allowed to evaporate. Solid dispersions prepared were crushed, pulverized and sifted through sieve number #40 and stored in desiccators. The results of immediate release formulation are shown in table 1.

Solubility measurements

To evaluate the solubility of CA in the presence and absence of Gelucire 50/13 or Poloxamer 188, saturation solubility measurements were conducted.[12,13] An excess amount of plain CA and dispersing powder were added to 20 ml of freshly prepared simulated gastric fluid (SFG) without enzyme in clean vials with continuous shaking at 25 ± 0.5ºC for 24 h to achieve equilibrium. The filtered solutions were suitably diluted and analyzed for CA at λ_{max} 281 nm using UV spectrophotometer (Shimadzu, model no. 1800, Switzerland). The results are shown in table 2.

Flowability and compressibility measurement

Solid dispersion granules were characterized for flow and compressibility by measuring Compressibility index (%), Hausner's ratio and angle of repose (Table 3 and 4). The term bulk density refers to a measure used to describe a packing of particles or granules. It is a

simple test to evaluate the flowability and the rate of packing. The equation for determining bulk density is.

$$\text{Bulk density} = \frac{\text{Mass}}{\text{Bulk volume}} \ldots\ldots\ldots\ldots\ldots (1)$$

The volume of the packing was determined in a 10 ml graduated cylinder. The cylinder was filled with a certain mass of the sample and the initial volume was measured and poured density was calculated. Pre-weighted amount of granule were weighted out and filled in a 10 ml measuring cylinder. The volume of the co-agglomerates was found out i.e. the bulk volume. Measuring cylinder was tapped. After a certain tapping no reduction of volume of powder occur. The volume of the powder at that time was noted down.[14]

$$\text{Tapped density} = \frac{\text{Mass}}{\text{Tapped volume}} \ldots\ldots\ldots\ldots\ldots (2)$$

The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material. Compressibility index (CI) values were determined according to the formula.

$$\text{CI} = \frac{(\text{Tapped density} - \text{Bulk density})}{(\text{Tapped density})} \text{x } 100 \ldots\ldots\ldots\ldots\ldots (3)$$

Hausner's ratio is determined by following formula.

$$\text{Hausner's Ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \ldots\ldots\ldots\ldots\ldots (4)$$

Hausner's ratio is used in a wide variety of industries as an indication of the flowability of a powder. Hausner's ratio greater than 1.25 is considered to be an indication of poor flowability. Angle of repose was determined by allowing the dispersion granules to flow through a funnel (with a 10 mm orifice diameter) and measuring the angle between the horizontal and the slope of the heap of granules. The radius (R) and height (H) of the pile was measured. Then the angle of repose (θ) was calculated using following formula. The results of flowability and compressibility data are summarized in table 3 and micrometric properties are illustrated in table 4.

$$\theta = Tan^{-1} \, H/R \ldots\ldots\ldots\ldots\ldots (5)$$

Preparation of mini tablets at different compaction pressure

Mini tablets were prepared by direct compression method. An accurate amount of the ingredients were mixed properly in a poly bag and were then fed into the die of an

instrumented pellet press to produce mini tablet. A punch of 6 mm diameter, with a dwell time of 2 sec and a compaction pressure of 0.5, 1, 2 and 3 ton was applied for preparing tablet.

Table 2: Solubility measurements of cefuroxime axetil solid dispersions of Gelucire 50/13, Poloxamer 188 and Sylysia 350.

Batch No.	Cefuroxime axetil	Gelucire 50/13	Solubility of SD CA+Gelucire 50/13 (mg/ml)*	Poloxamer 188	Solubility of SD CA+ Poloxamer 188 (mg/ml)*	Sylysia 350	Solubility of SD CA+ Sylysia 350 (mg/ml)*
A0	1	--	0.1215±0.003	--	0.1215±0.003	--	0.1215±0.003
A1	1	0.25	0.3418±0.004	0.25	0.3534±0.005	0.25	0.4255±0.002
A2	1	0.5	0.3697±0.002	0.5	0.3744±0.006	0.5	0.4674±0.005
A3	1	0.75	0.4023±0.006	0.75	0.4186±0.003	0.75	0.6674±0.003
A4	1	1	0.4255±0.003	1	0.4813±0.005	1	0.7139±0.007
A5	1	1.25	0.4744±0.005	1.25	0.6465±0.008	1.25	0.7837±0.002
A6	1	1.5	0.5139±0.007	1.5	0.6581±0.007	1.5	0.8581±0.004
A7	1	1.75	0.5627±0.002	1.75	0.7232±0.005	1.75	0.9093±0.003
A8	1	2	0.6604±0.003	2	0.7627±0.002	2	0.9488±0.005
A9	1	3	0.7279±0.005	3	0.7930±0.006	3	0.9953±0.007
A10	1	4	0.7837±0.002	4	0.9023±0.004	4	1.0465±0.003
A11	1	5	0.8186±0.003	5	1.0093±0.007	-	-

* Mean ± SD, n=3, n is the number of observations.

Table 3: Flowabilty and Compressibility data.

Batch no	Dispersion (parts)	Neusilin US2 (parts)	Bulk property		
			Angle of repose (^{0})*	Compressibility index (%) *	Hausner's ratio*
A0	--	--	40±0.98	35±0.52	1.56±0.44
A1	2.5	0.25	#	#	#
A2	2.5	0.5	32±2	23±2	o.56±0.12
A3	2.5	0.75	25±3	16±2	0.42±0.15

Not possible to determine because of sticky nature of the dispersion granule.

* Mean ± SD, n=3, n is the number of observations.

Table 4: Micromeritic properties of formulations A0 to A11

Batch no	Bulk property		
	Angle of repose (^{0})*	Compressibility index (%) *	Hausener's ratio*
A0	40±0.98	35±0.52	1.56±0.44
A1	19±0.87	23±1.02	0.56±0.56
A2	21±1.21	20.5±0.86	0.62±1.02
A3	22.5±2.02	25±0.58	0.55±1.52
A4	22±2.56	24±0.78	0.61±2.01
A5	21±1.05	25±0.88	0.59±1.01
A6	21.5±1.95	26±0.51	0.57±0.48
A7	19±1.86	21±1.08	0.56±0.56
A8	21±1.29	21.5±0.81	0.68±0.98
A9	22.5±1.07	25±0.86	0.59±1.45
A10	22±2.15	24±0.93	0.63±2.08
A11	21±1.51	23±0.71	0.65±1.02

* Mean ± SD, n=3, n is the number of observations

Quality control test for solid dispersions and immediate release mini-tablet

Drug content of solid dispersion

An amount equivalent to 50 mg of CA solid dispersion granule were weighed and extracted in SGF using an ultra sound bath for 10 min. after filtration through membrane filter and suitable dilutions, samples were analyzed spectrophotometrically at λ_{max} 281 nm.[15,16]

Drug content of tablet

Twenty tablets were weighed and finely powdered. An amount of tablet, powder equivalent to 100 mg of CA was accurately weighed and transferred in a 100 ml volumetric flask and 50 ml of simulated gastric fluid without enzyme was added. The solution was subjected to sonication for 10 min for complete extraction of drugs and the solution was made up to the mark with the same solution to obtain a concentration of 5 mg/ml. The above solution was diluted using the same solution to get a concentration of 100µg/ml and absorbance was measured at λ_{max} 281 nm using a UV visible spectrophotometer. The actual concentration of the sample was determined from the calibration curve of CA prepared using simulated gastric fluid without enzyme.[15]

Hardness test

The hardness of the tablets was determined with a digital tablet hardness tester (Electrolab, India). Ten tablets were used in each test and the mean hardness was calculated.[14]

$$\text{Mean hardness} = \frac{\text{Total hardness of 10 tablets}}{10} \dots\dots\dots\dots\dots\dots (6)$$

Friability test

The friability of the tablets was evaluated with a digital friabilator (Electrolab, India). Twenty tablets were weighed prior to placing them in the friabilator chamber and at the end of the test, their weight was also recorded. Finally, the loss in weight was calculated[14],

$$\% \text{ Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \text{x } 100 \ldots\ldots\ldots\ldots (7)$$

Weight uniformity

For weight uniformity test, twenty tablets were randomly selected and weighed using a Class A electronic weight balance (Electrolab, India) and weight variation (%) was calculated[14],

$$\text{Weight uniformity} = \frac{\text{Average weight} - \text{indivisual weight}}{\text{Average weight}} \ldots\ldots\ldots\ldots (8)$$

Disintegration test

To test the disintegration time one tablet was placed in each tube, and the basket rack assembly was positioned in a one litre beaker of SGF, at 37 $\pm 2^0$C, such that the tablet remain 2.5 cm from the bottom of the beaker. The disintegration time was noted. The calculated data for a disintegration test of formulations of CA with Sylysia 350, Poloxamer 188 & Gelucire 50/13 are summarized in table 5.

X-ray diffraction

X-ray powder diffraction patterns were obtained at room temperature using a XPERT-PRO with a Cu anode and a graphite monochromator, operated at a voltage of 35 kV and a current of 20 mA. The samples were analyzed in the 2θ angle range of 5–50° and the process parameters were set as scan-step size of 0.02° (2θ) and scan-step time of 25s.[17]

In vitro dissolution test

Dissolution profiles of CA from solid dispersion granules and mini tablets were determined using a USP Type II dissolution apparatus (Disso-USP, Electrolab, India) at 50 rpm. The dissolution medium consisted of SGF without enzyme. Temperature maintained 37 $\pm 0.5^0$C throughout the period of dissolution test. The rotating rate of the paddle was adjusted to 50 rpm. With a predetermined sampling period (5', 10', 15', 30', 45' & 60') min intervals, 5 ml of samples was withdrawn and filtered through a Whatman's filter paper. The equivalent volume of the medium with the same temperature was added to the dissolution vessel. The absorbance values of the filtrate at the wavelength of 281 nm were determined

spectrophotometrically by UV-Vis spectrophotometer (Shimadzu, Japan) after suitable dilution.

Table 5: Quality control tests of formulations of CA with Sylysia 350, Poloxamer 188 & Gelucire 50/13.

Batch no.	Hardness (kg/cm^2) *	D.T (min) *	Friability (%)*	Weight variation	Drug content (%)*
Quality Control Tests of Formulations of CA & Sylysia 350					
F1	6.2±1.2	Not disintegrate	0.34	PASS	98.5±0.46
F2	6.8±1.5	9.45±0.12	0.28	PASS	98.1±0.3
F3	7.2±1.7	5.27±0.32	0.36	PASS	97.9±0.24
F4	7.2±0.56	3.41±0.26	0.42	PASS	99.1±0.67
F5	6.5±0.61	2.27±0.51	0.43	PASS	97.6±0.5
F6	6.4±0.12	2.23±0.46	0.35	PASS	97.3±0.29
F7	6.6±0.23	2.21±0.14	0.36	PASS	98.1±0.21
F8	6.1±0.33	2.18±0.57	0.39	PASS	98.6±0.12
F9	6.7±0.09	2.16±0.17	0.33	PASS	98.9±0.34
F10	6.2±0.71	2.14±0.62	0.37	PASS	97.9±0.89
Quality Control Tests of Formulations of CA & Poloxamer 188					
F1	4.2±1.3	Not disintegrate	0.37	PASS	97.5±0.61
F2	4.8±1.9	Not disintegrate	0.31	PASS	98.5±0.43
F3	5.2±1.8	Not disintegrate	0.33	PASS	97.8±0.94
F4	4.2±0.59	Not disintegrate	0.38	PASS	98.9±0.63
F5	5.5±0.51	Not disintegrate	0.43	PASS	97.8±0.51
F6	4.4±0.19	Not disintegrate	0.45	PASS	97.3±0.91
F7	4.6±0.24	Not disintegrate	0.34	PASS	98.1±0.29
F8	5.1±0.39	Not disintegrate	0.37	PASS	98.8±0.26
F9	4.7±0.45	29.16±0.19	0.33	PASS	98.2±0.87
F10	5.2±0.91	25.14±0.12	0.39	PASS	98.9±0.12
Quality Control Tests of Formulations of CA & Gelucire 50/13					
F1	4.5±1.41	Not disintegrate	0.39	PASS	98.7±0.75
F2	4.3±0.92	Not disintegrate	0.33	PASS	98.8±0.49
F3	5.2±0.84	Not disintegrate	0.36	PASS	97.9±0.98
F4	4.8±0.53	Not disintegrate	0.38	PASS	98.1±0.69
F5	5.1±0.58	Not disintegrate	0.41	PASS	98.8±0.67
F6	4.9±0.98	Not disintegrate	0.44	PASS	97.9±0.99
F7	4.6±0.29	29.19±0.18	0.39	PASS	98.4±0.27
F8	5.1±0.87	26.14±0.14	0.35	PASS	98.9±0.61
F9	4.9±0.48	24.16±0.21	0.37	PASS	98.2±0.87
F10	5.1±0.14	21.17±0.23	0.42	PASS	98.5±0.14

* Mean ± SD, n=3, n is the number of observations

Dissolution efficiency (% DE)

The percent dissolution efficiency (% DE) was also computed to compare the relative performance of various concentrations of superdisintigrant (cross povidone) in the formulations (Table 6). The % DE of a pharmaceutical dosage form is defined as the area under the dissolution curve up to a certain time, t, expressed as a percentage of the area of the rectangle described by 100 % dissolution at the same time.[18] The % DE can be calculated from.

$$\% \text{ DE} = \frac{\int_0^t Y dt}{Y_{100} t} * 100 \text{ ---------- (9)}$$

Where Y is the percent drug dissolved at time t.

Mean dissolution time (MDT)

To understand the extent of CA dissolution rate enhancement from its formulations, the dissolution data were used to calculate the mean dissolution time (MDT).[19] The MDT can be calculated by using following equation.

$$MDT_{\text{in vitro}} = \frac{\sum_{i=1}^{n} T_{mid}\, \Delta M}{\sum_{i=1}^{n} \Delta M} \text{ ---------- (10)}$$

Here, i is the dissolution sample number, n is the number of dissolution sampling times, T_{mid} is the midpoint between times T_i and T_{i-1}, and ΔM is the amount of CA dissolved between times T_i and T_{i-1} (Table 6 and 7).

Correlation coefficient for Hixson Crowell's cube-root equation will be;

$W0^{1/3} - Wt^{1/3} = Kt$ ---------- (11)

W0= Initial amount of drug present in the Matrix

Wt= Amount of the drug remaining to dissolved at time't'

K= Dissolution rate constant.

All the data for dissolution efficiency (DE), mean dissolution time (MDT) and correlation coefficient for Hixson Crowell's equation for different formulations are shown in table 7.

Table 6: Tabulation for dissolution efficiency (DE), mean dissolution time (MDT) and Correlation coefficient for Hixson Crowell's equation of formulations of CA & Sylysia 350

Formulation code	% DE_5	% DE_{10}	% DE_{15}	MDT (min)	Hixson Crowell's (r^2)
CA	7.46	8.63	9.75	10.43	0.972
PM of CA+Sylysia 350	25.45	29.62	32.75	9.67	0.983
SD of CA+Sylysia 350	50.55	51.61	53.35	5.98	0.991
Mini tablet	9.75	10.45	11.86	8.95	0.967
F4	51.95	56.15	56.85	5.11	0.995

Table 7: Tabulation for dissolution efficiency (DE), mean dissolution time (MDT) and correlation coefficient for Hixson Crowell's equation of different formulations.

Formulations	% DE_5	% DE_{10}	% DE_{15}	MDT (min)	Hixson Crowell's (r^2)	Formulations	% DE_5	% DE_{10}	% DE_{15}	MDT (min)	Hixson Crowell's (r^2)
CA	7.46	8.63	9.75	10.43	0.972	CA	7.46	8.63	9.75	10.43	0.972
PM of CA+Poloxamer 188	9.42	11.15	11.85	9.87	0.983	PM of CA+Gelucire 50/13	11.53	14.65	16.35	9.84	0.991
PM of CA+Polxamer 188+ Neusillin US2	14.65	17.05	19.15	9.23	0.992	PM of CA+ Gelucire 50/13+ Neusillin US2	13.67	18.16	21.64	9.65	0.989
SD of CA+Poloxamer 188	30.65	32.75	36.63	5.86	0.987	SD of CA+ Gelucire 50/13	30.34	34.85	38.74	6.12	0.976
SD of CA+Polxamer 188+ Neusillin US2	38.35	43.65	46.74	5.34	0.994	SD of CA+ Gelucire 50/13+ Neusillin US2	40.16	43.65	47.05	5.87	0.987
Mini-Tablet	8.72	9.47	10.87	8.15	0.958	Mini-Tablet	8.34	9.15	10.23	9.54	0.954
F10	14.32	17.05	19.15	6.54	0.967	F10	11.85	12.96	14.62	8.98	0.932

RESULTS AND DISCUSSION

From the solubility data it was confirmed that six fold increase in the solubility of the drug. The improved solubility of CA from solid dispersions prepared using the melt dispersion method can be explained by the improved usability of the CA particles in aqueous solution from Gelucire 50/13. Surface active power improves the solubility and wettability of active pharmaceutical ingredient. The solubility increased with an increase in the ratio of Gelucire: drug. Although solid dispersions have the potential to enhance the dissolution of poorly water-soluble drugs, but have some challenging factors like difficult in a pulverization, poor compressibility, and poor flow ability of solid dispersions. The high-energy amorphous state of the drug in solid dispersions tends to revert to the less soluble crystalline form of storage this is another drawback of this process.[11] As maximum improvement in solubility was

observed for the formulation A11 which contain the drug to carrier (Gelucire 50/13 or Poloxamer 188) in the ratio of 1:5. But for the suitability of the formulation of mini-tablets, we selected formulation A8, which increases four folds of solubility of the drug, contain drug to carrier (Gelucire 50/13 or Poloxamer 188) in the ratio of 1:2. Similarly, from the solubility data that there is an eight fold increase in the solubility of the drug. The improved solubility of CA from solid dispersions prepared using the melt dispersion method can be explained by the improve wettability of the CA particles in aqueous solution from Poloxamer 188. Surfactive power improves the solubility and wettability of active pharmaceutical ingredient. The comparison graph of the SD of CA with Sylysia 350, Poloxamer 188 & Gelucire 50/13 are depicted in Fig-1.

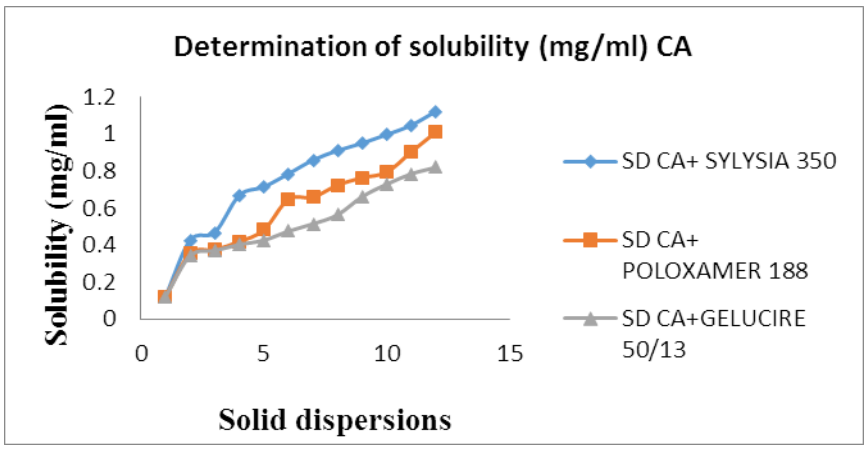

Fig-1: Comparison graph of SD of CA with Sylysia 350, Poloxamer 188 & Gelucire 50/13.

The immediate release formulation using solid dispersions of CA & Sylysia 350, CA & Poloxamer 188 and CA & Gelucire 50/13 as shown in Table 1 and solubility measurements of cefuroxime axetil solid dispersions of Gelucire 50/13, Poloxamer 188 and Sylysia 350 as shown in Table 2. The value of the angle of repose, C. I and H.R for pure drug (CA) revealed that the flowability and compressibility were not within the theoretical range for processing into tablet dosage form (Table 3 & 4). The solid dispersions of CA and Glacier 50/13 or Poloxamer 188 were sticky in nature. In order to improve the flowability of the dispersion, an adsorbent Neusilin US2 was added in different proportion. The amorphous and adsorbent nature of Neusilin US2 decrease the rate of reversion of the dispersed drug to its crystalline state Due to its high oil adsorption capacity, high specific surface area it also improves compressibility and flowability. In case of formulation A1, an amount of 0.25 parts of Neusilin US2 was not sufficient to convert into flowable dispersion granule. In case of

formulation A2, even though the sticky dispersion was converted into a dispersion granule but of angle of repose, C.I and H.R value revealed that they are not within the theoretical range for processing into tablet dosage form. Formulation A3 showed that the value of angle of repose, C.I and H.R were within the the theoretical range for processing into tablet dosage form. Hence, an amount of 0.75 parts of Neusilin US2 was found to be the optimum quantity for converting the sticky dispersion of drug into a freely flowable dispersion granule.[20] The improved solubility of Cefuroxime axetil from solid dispersions prepared using a solvent evaporation method can be explained by the rapid dissipation of the drug from Sylysia 350 surfaces. The addition of SGF to the solid dispersion results in desorption of drug from Sylysia 350 surface. This is the result of stronger interactions between the Sylysia 350 and SGF than those between Sylysia 350 and drug. The drug is adsorbed to certain extent as a thin layer or small particles on to the pores of Sylysia 350. The high specific area of these particles contributes to the improved solubility of solid dispersions compared to pure drug. As maximum improvement in solubility was observed for the formulation A11 which contain drug to carrier (Sylysia 350) in the ratio of 1:5. But for the suitability of the formulation of mini-tablets, we selected formulation A9 which increases seven. The value of angle of repose, C.I and H.R for pure drug CA revealed that the flowability and compressibility not within the theoretical range for processing into tablet dosage form. From the above three solid dispersion, SD of CA + Sylysia 350 having the better increase in the solubility of CA. From this dissolution data, we obtained that only 23% of drug release in 1 hr dissolution of pure drug. From the dissolution data, 100% drug release in 5 minutes in case of solid dispersion of CA & Sylysia 350. The plot for pure drug, PM, SD & mini-tablets CA & Sylysia 350 are shown in fig. 2.

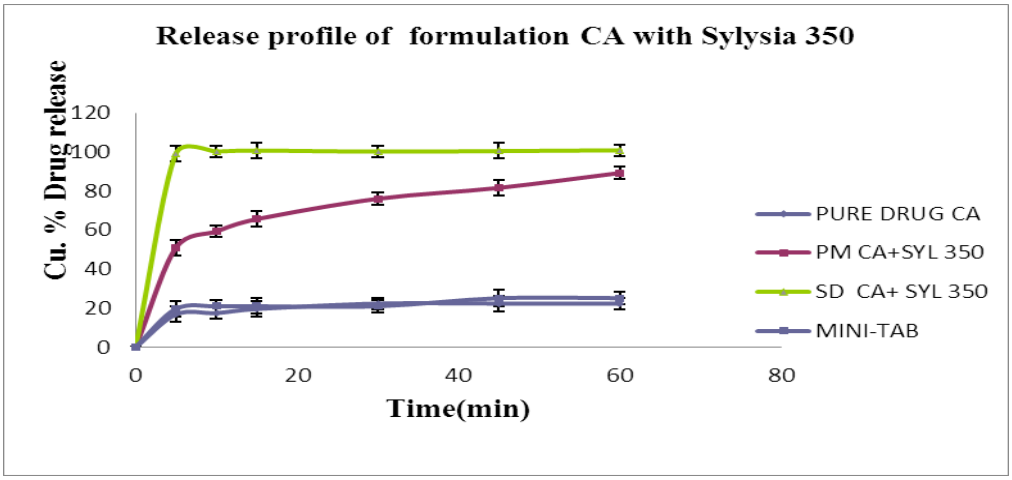

Fig-2: Graph of pure drug, PM, SD & mini-tablets ca & sylysia 350.

From the dissolution data, 80% drug release in 1 h in case of Physical mixture of CA & Sylysia 350. When the solid dispersion granules of CA and Sylysia 350 were compressed into a mini-tablet then the rate of penetration of dissolution fluid into the tablet decreases i.e. that leads to a decrease in dissolution rate. From this dissolution data, we obtained that only 23% of drug release in 1 h dissolution of pure drug CA. From the dissolution data, 96% drug release in1 hr in case of solid dispersions of CA & Poloxamer 188. From the dissolution data, nearly 100% drug release in 45 minutes in case of solid dispersion of CA, Poloxamer 188 & Neusilin US2. The plot for pure drug, PM, SD & mini-tablets CA & Poloxamer 188 are depicted in fig. 3.

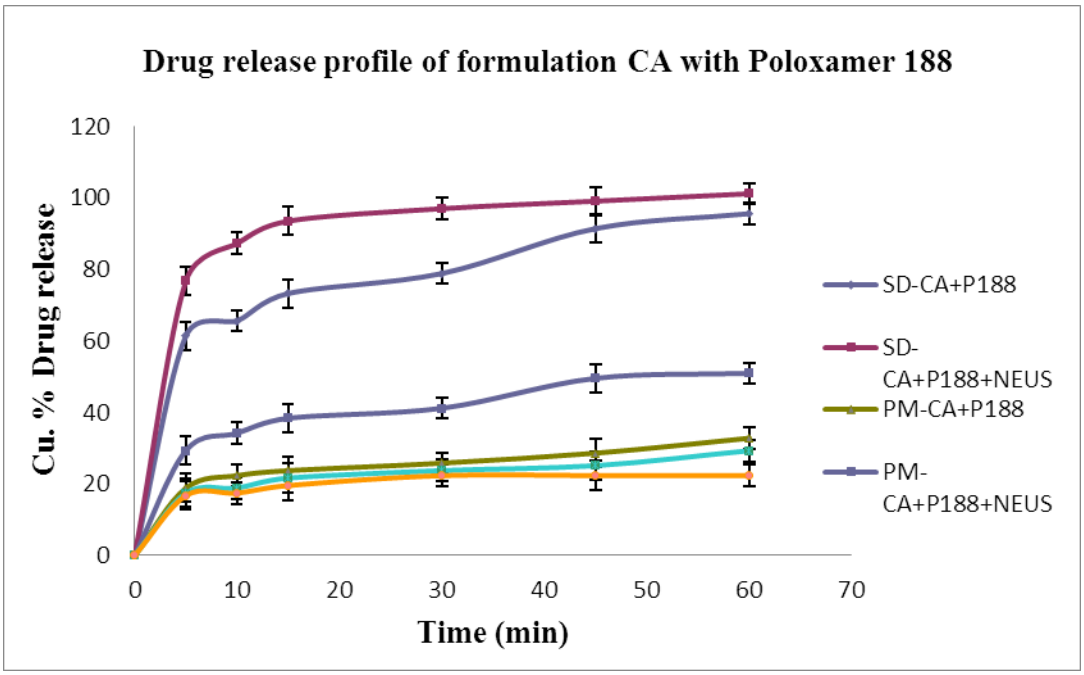

Fig-3: Graph of pure drug, PM, mini-tablet & poloxamer 188 based solid dispersions.

From the dissolution data, 33% drug release in 1 hr in case of physical mixture of CA & Poloxamer 188. From the dissolution data, 51% drug release in 1 h in case of physical mixture of CA, Poloxamer 188 & Neusilin US2. When the solid dispersion granules of CA and Poloxamer 188 was compressed into a mini-tablet then the rate of penetration of dissolution fluid into the tablet decreases i.e. that leads to an decrease in dissolution rate. From this dissolution data, we obtained that only 23% of drug release in 1h issolution of pure drug CA. From the dissolution date, 95% drug release in1 hour in case of Solid dispersion of CA & Gelucire 50/13. From the dissolution data, nearly 100% drug release in 45 minutes in case of solid dispersion of CA, Gelucire 50/13 & Neusilin US2. The plot for pure drug, PM, SD & mini-tablets CA & Gelucire 50/13 are depicted in fig. 4.

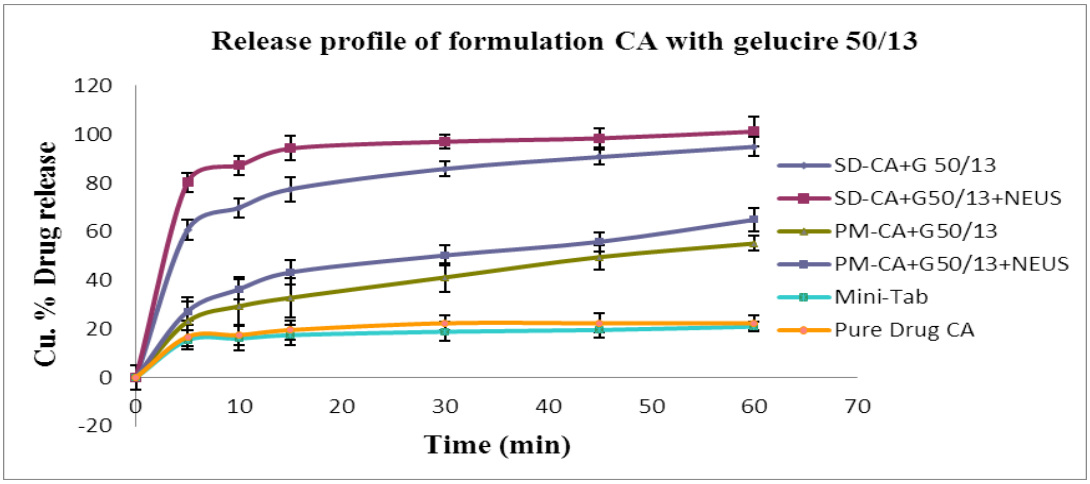

Fig-4: Graph of pure drug, PM, SD & mini-tablet CA & Gelucire 50/13.

From the dissolution data, 55% drug release in case of physical mixture of CA & Gelucire 50/13 and 65% drug release within 1 hr in case of physical mixture of CA, Gelucire 50/13 & Neusilin US2. When the solid dispersion granules of CA and Gelucire 50/13 were compressed into a mini-tablet then the rate of penetration of dissolution fluid into the tablet decreases i.e. that leads to a decrease in dissolution rate. When the solid dispersion granules of CA and Sylysia 350 or Gelucire 50/13 and Poloxamer 188 were compressed into a tablet then the rate of penetration of dissolution fluid into the tablet decreases i.e. that leads to a decrease in dissolution rate. Increase in compaction pressure of mini-tablet from 0.5 ton to 3 ton, the dissolution rate of CA decreased with increased pressure of mini-tablets. The plot for effect of pressure CA & Sylysia 350 or Gelucire 50/13 and Poloxamer 188 are shown in fig. 5, 6 & 7 respectively.

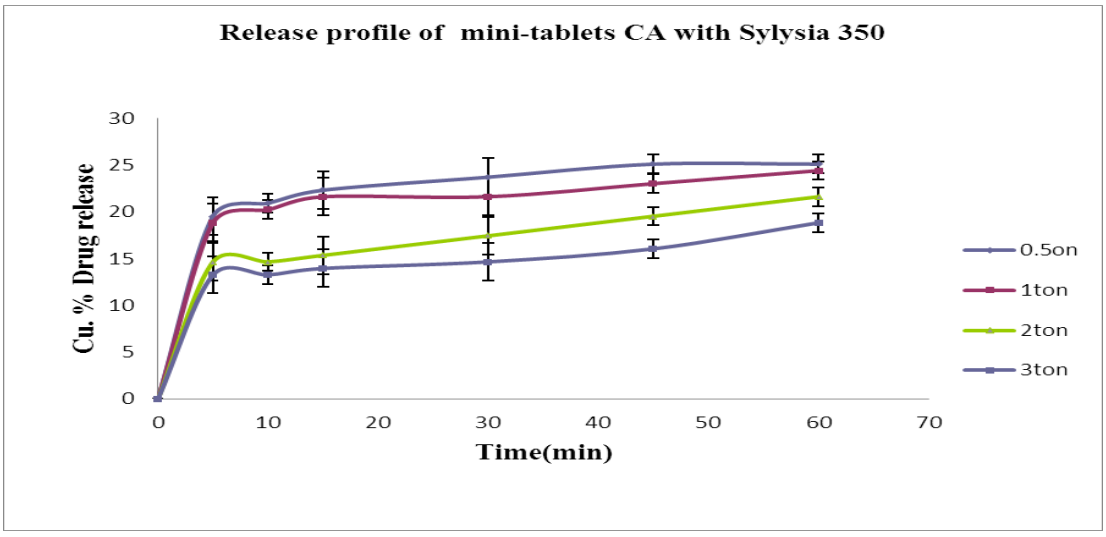

Fig-5: Graph of effect of pressure on CA & Sylysia 350 based mini-tablets

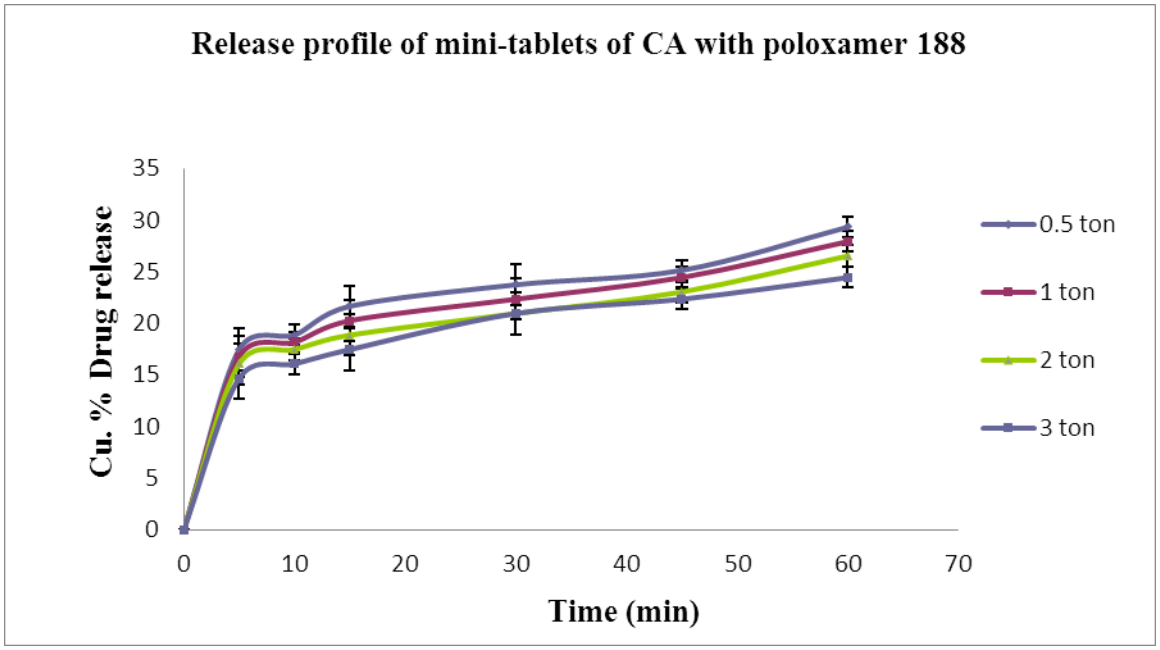

Fig-6: Graph of effect of pressure on CA & poloxamer 188 based mini-tablets.

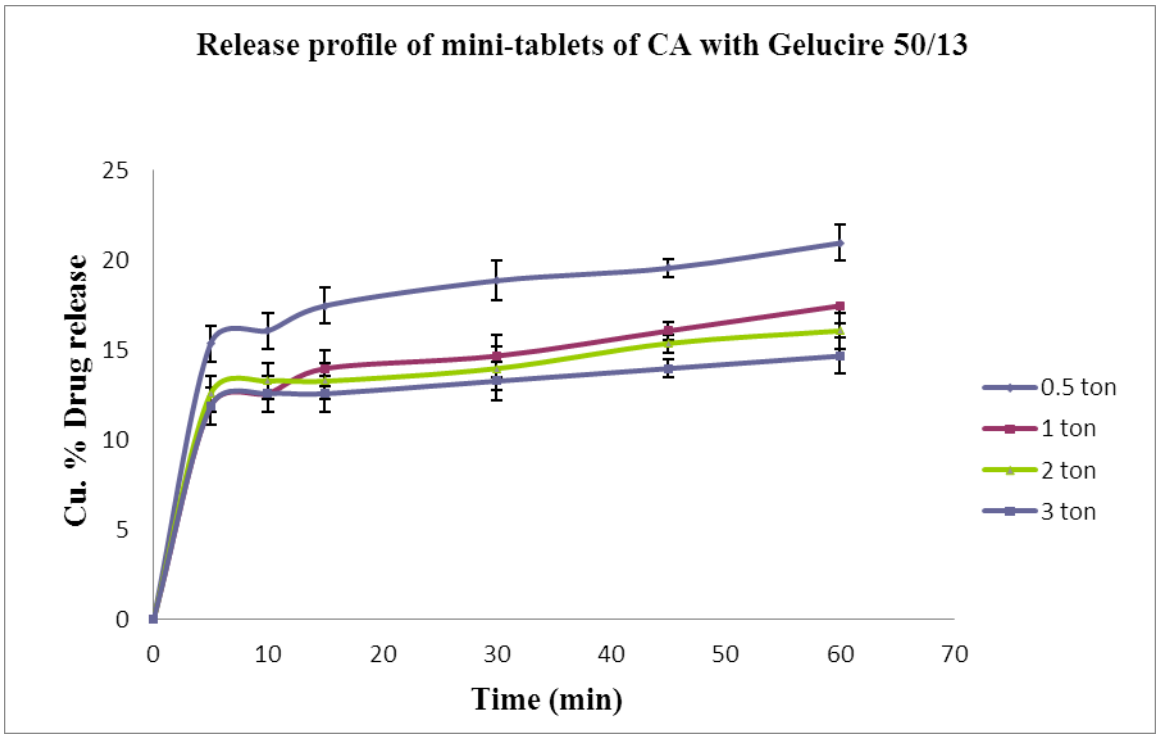

Fig-7: Graph of effect of pressure on CA & Gelucire 50/13 based mini tablets.

The plot for effect of pressure on CA & Gelucire 50/13 based mini-tablets are shown in Fig. 7. Drug content values ensured uniform mixing of CA, Sylysia 350 and other excipients. Hardness of the tablets was in the range of 6.1 to 7.2 kg/cm^2. This reveals that the required compressibility was impacted by Sylysia 350 and MCC. Friability values were in the range of 0.28% and 0.43%, which ensures no loss of material from the surface or edge of tablets. All

the formulations passed weight variation test which is indicative of good flowability of solid dispersion granules. From D.T. study, formulation F1 which was not disintegrated within 30 minutes. As the proportion of Cross Povidone increased from 1 to 10% per tablet i.e. from the formulation. F2 to F10 the disintegration time decreased from 9.45 minutes to 2.14 minutes. This was due to its rapidly dispersing and swelling nature in contact water. Drug content values ensured uniform mixing of CA, Poloxamer 188, Neusilin US2 and other excipients. Hardness of the tablets was in the range of 4.2 to 5.5 kg/cm^2. This reveals that the required compressibility was impacted by Neusilin US2 and MCC. Friability values were in the range of 0.31% and 0.45%, which ensures no loss of material from the surface or edge of tablets. This may be attributed to the waxy nature of Poloxamer 188. All the formulations passed weight variation test which is indicative of good flowability of solid dispersion granules. From D.T. Study, Formulation F1 without cross povidone not disintegrated within 30 minutes. As the proportion of cross povidone increased from 1% to 10% of CP per tablet i.e. from formulation. F2 to F8 not disintegrating within 30 minutes. But F9 & F10 formulations were disintegrated within 30 minutes. Drug content values ensured uniform mixing of CA, Gelucire 50/13, Neusilin US2 and other excipients. Hardness of the tablets was in the range of 4.2 to 5.2 kg/cm^2 (Table 5). This reveals that the required compressibility was impacted by Neusilin US2 and MCC. Friability values were in the range of 0.33 to 0.44%, which ensures no loss of material from the surface or edge of tablets. This may be attributed to the waxy nature of Gelucire 50/13. All the formulations passed weight variation test which is indicative of good flowability of dispersion granules. From D.T. study, formulation F1 without cross povidone not disintegrated within 30 minutes. As the proportion of cross povidone increased from 1 to 10% of CP per tablet i.e. from formulation. F2 to F6 not disintegrated within 30 minutes. But F7 to F10 formulations were disintegrated within 30 minutes. X-RD pattern of CA indicate its amorphous nature, while gelucire-50/13 shows a semi-crystalline nature which was shown its X-RD plot (Fig. 8).

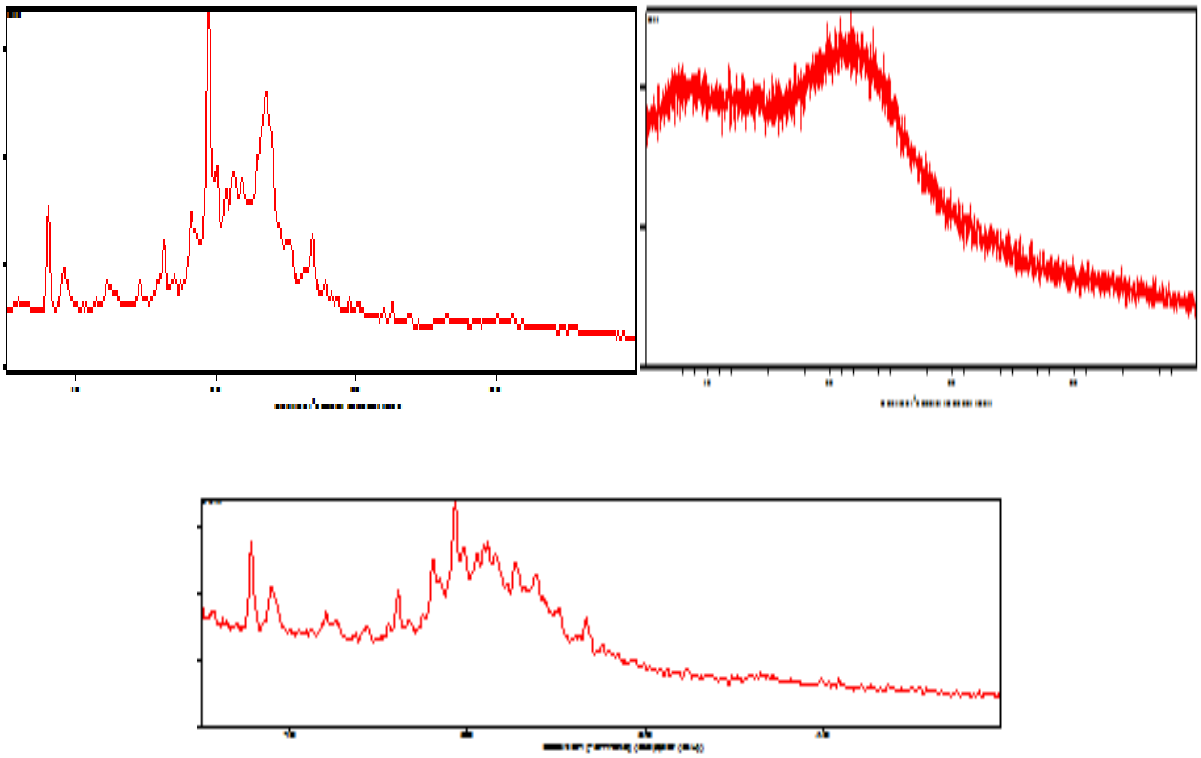

Fig-8: X-ray diffraction spectrum.

Solid dispersion (1:1.25) indicates the reversion of the amorphous form of CA in the matrix of gelucire-50/13. Furthermore the presence of Neusilin US2 could less likely promote the reversion of the amorphous drug to crystalline state on storage of the solid dispersion because of its amorphous.[11] From this dissolution data, it was observed that only 23% of drug was dissolved in 1 h of dissolution study. From the dissolution data formulation F1 (without CP) only release 43% drug release in 1 hr. The improvement in dissolution rate of formulation F2 & F3 presence of Cross povidone (CP), 100% drug release within in 15 minute in case formulation F2 & nearly 100% drug release within in 10 min in F3. Increase in the % of CP, the formulations F4-F10, 100% of drug release within 5 minutes. Cross povidone produces faster disintegration because of high capillary activity & pronounced hydration capacity, with little tendency to form gels.[21] The DE_5, DE_{10} and DE_{15} values are presented in Table 6 & 7. The DE values for CA, PM and mini-tablet were significantly lower than formulation SD and F4. Dissolution onset of F4 was very fast and among the formulations CA, PM, SD and mini-tablet had maximum value of DE_5, DE_{10}, and DE_{15}. Formulation F4 and SD of CA with Sylysia 350 showed nearly similar dissolution efficiency values. The plot of pure drug and mini-tablets of CA & Sylysia 350 are shown in fig. 9.

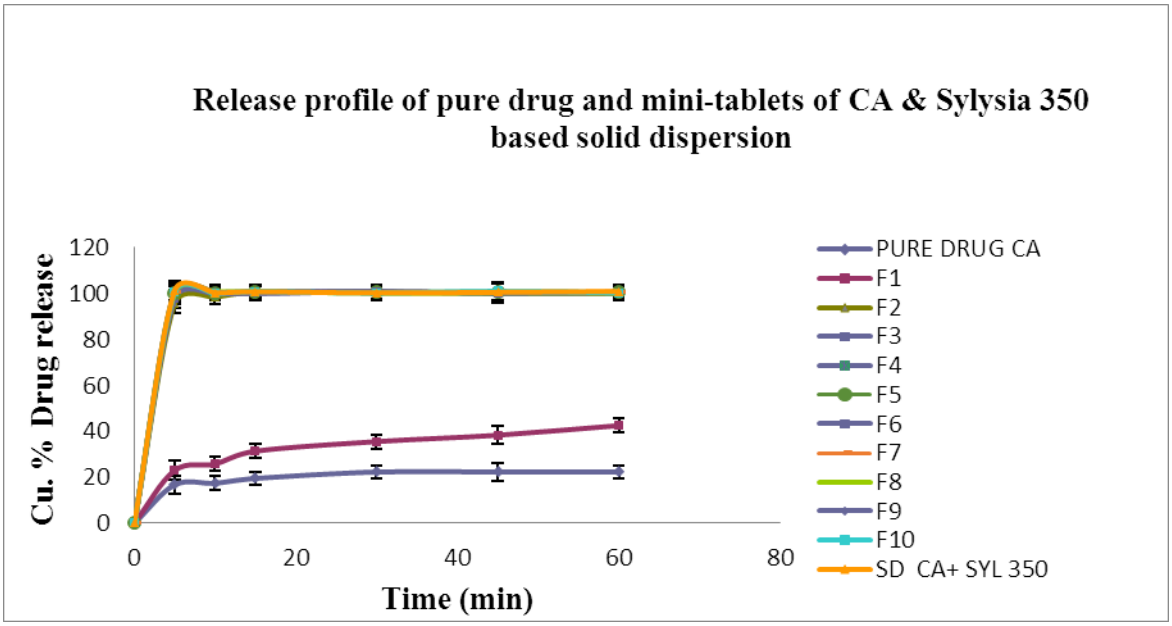

Fig-9: Graph of pure drug and mini-tablets of CA & Sylysia 350 based solid dispersion.

This was due to quick disintegration (2 min) of the F4 and SD. The MDT for CA is 10.43 min; it decreased to 5.98 and 5.11 min for SD and F4 respectively. This suggests that dissolution of CA from these two formulations was faster compared to other formulations**.** Formulation, F4 showed more than 99% CA release in 5 min hence tablet formulation F4 is a rapidly dissolving tablet as per WHO. Correlation coefficient for Hixson Crowell's equation was higher for formulation PM, SD and F4 suggesting that the rate of dissolution increased with an increase in surface area. From this dissolution data, 23% of drug release in 1 h dissolution of pure drug CA. From the dissolution data formulation F1 (without CP) only release 29% drug release in 1 hr. Increase in the % of CP, the formulations F2-F10, drug release only increase 36% to 53% in 1 h. The observed enhancement may be attributed to the effects of solid dispersion and surface dispersion. Poloxamer 188 has an HLB value of 29 and Poloxamer 188 are the block co-polymer of POE & POP (Poly oxy propylene) and is expected to solubilize the hydrophobic drug CA in solid state.[22] Simultaneous presence of Neusillin US2 increases the effective surface area over which drug is spread. The DE_5, DE_{10}, and DE_{15} values of different formulations are presented in table 7. The DE values for CA, PM, Mini-tablet and F10 were significantly lower than formulation SD. Dissolution onset of SD was very fast and among the formulations CA, PM, Mini-tablet and F10 had maximum value of DE_5, DE_{10}, and DE_{15} formulation SD of CA with Poloxamer 188 & Neusilin US2 showed high dissolution efficiency values. Drug release profile of formulations of mini tablets of CA with polaxomer 188 is depicted in fig.10.

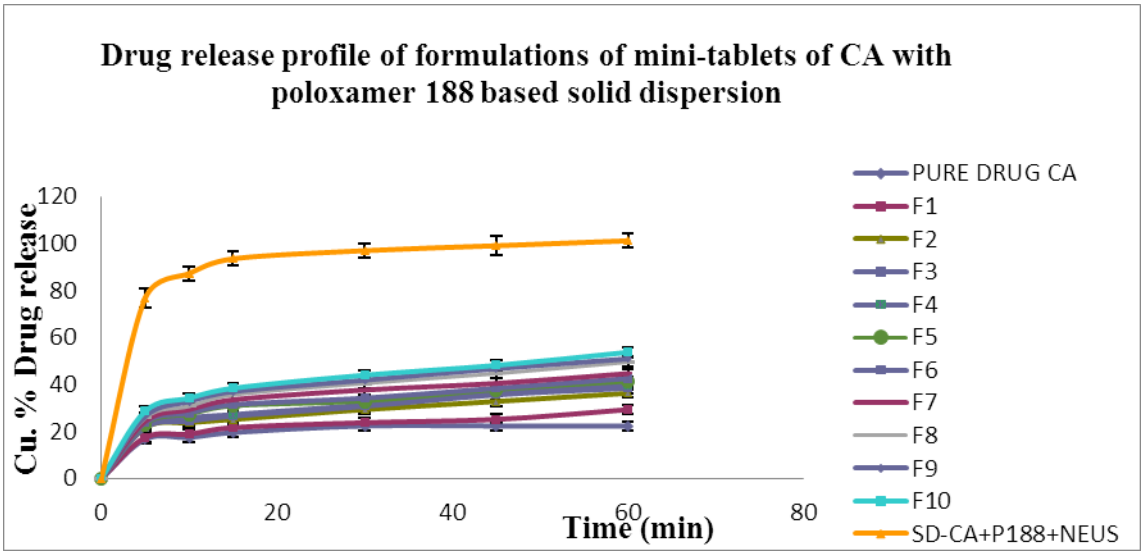

Fig-10: Graph of pure drug and mini-tablets of CA & poloxamer 188 based solid dispersion.

This was due to quick dissolution of SD. The MDT for CA is 10.43 min; it decreased to 5.86 and 5.34 min for SD of CA with Poloxamer 188 and SD of CA, Poloxamer 188 & Neusillin US2 respectively. This suggests that dissolution of CA from these SD formulations was faster compared to other formulations. Correlation coefficient for Hixson Crowell's equation was higher for formulation PM and SD, suggesting that the rate of dissolution increased with an increase in surface area. From this dissolution data, we obtained that only 23% of drug release in 1 h dissolution of pure drug CA. From the dissolution data formulation F1 (without CP) only release 20% drug release in 1 h. Increase in the % of CP, the Formulations F2-F10, drug release only increase 21% to 34% in 1 h. The observed enhancement may be attributed to the effects of solid dispersion and surface dispersion. Gelucire 50/13 has an HLB value of 13 and is expected to solubilize the hydrophobic drug CA in solid state. The simultaneous presence of Neusillin US2 increases the effective surface area over which drug is spread. The DE_5, DE_{10}, and DE_{15} values are presented in Table 7. The DE values for CA, PM, Mini-tablet and F10 were significantly lower than formulation SD. Dissolution onset of SD was very fast and among the formulations CA, PM, Mini-tablet and F10 had maximum value of DE_5, DE_{10}, and DE_{15} formulation SD of CA with Gelucire 50/13 & Neusilin US2 showed high dissolution efficiency values. The pure drug and mini-tablets of CA & Gelucire 50/13 are depicted in fig 11.

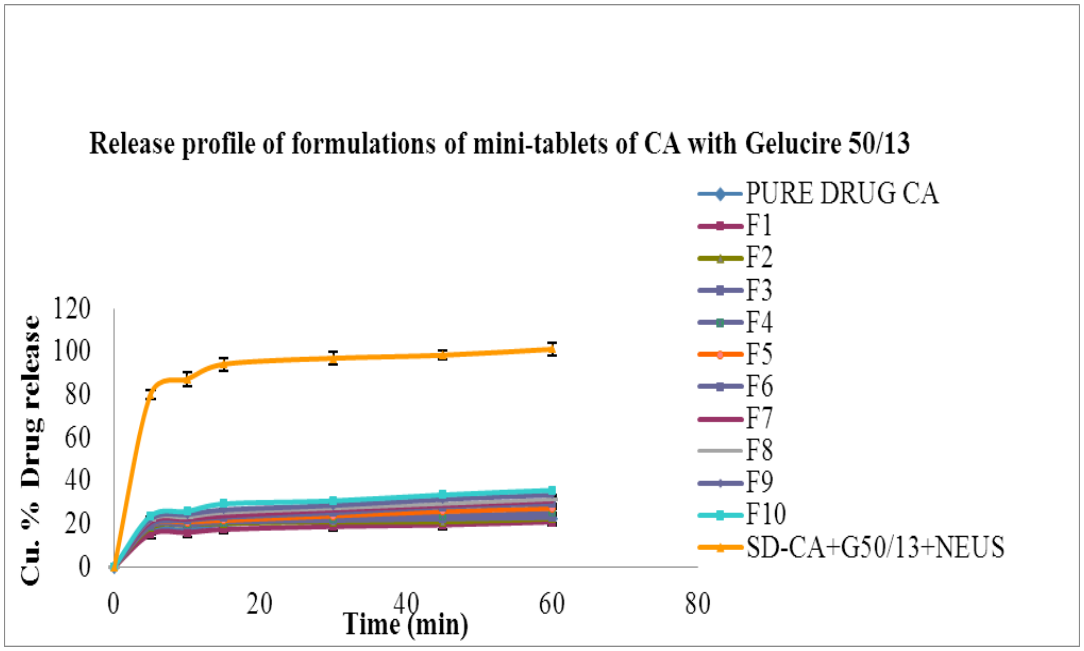

Fig-11: Graph of pure drug and mini-tablets of CA & Gelucire 50/13.

This was due to quick dissolution of SD. The MDT for CA is 10.43 min; it decreased to 6.12 and 5.87 min for SD of CA with Poloxamer 188 and SD of CA, Poloxamer 188 & Neusillin US2 respectively. This suggests that dissolution of CA from the formulation SD was faster compared to other formulations. The correlation coefficient for Hixson Crowell's equation was higher for formulation PM and SD, suggesting that the rate of dissolution increased with an increase in surface area.

CONCLUSIONS

From the above research, based upon the solubilty and in vitro dissolution kinetic study parameters, it was concluded that formulation of cefuroxime axetil with Sylysia 350 based mini tablets were found to be more appropriate and preeminent one, to be used as a hydrophilic carrier to accomplish immediate release of drug. Cefuroxime axetil tablets were proficiently formulated by direct compression process and incorporation of these selected hydrophilic grade of release modifiers in the process was found to be beneficial in enhancing solubility and in-vitro performance of the drug. The technique was carried out by a variety of intermediate such as in vitro USP dissolution profile, to count up physical and chemical properties as well as parameters of drug release kinetics. Further studies such as the X-RD pattern revealed its amorphous and semi-crystalline characteristics. This approaches for solubility enhancement are absolutely recommended for future forecast. From the above study, it was observed that, total three combination of formulations were prepared that is

mini-tablet of CA with Sylysia 350, mini-tablets of CA with Poloxamer 188 and mini-tablets of CA with Gelucire50/13**.** In this above formulation equal % of superdisintigrant (CP) was added. From the dissolution profile, ultimately it was achieved that the formulation of CA with Sylysia 350 mini-tablets were suitable for the immediate release tablet formulation as the drug release 100 % within 5 min for formulation F4, hence the anticipated objective of the current research was successfully achieved.

Conflict of interest

Authors declare no conflict(s) of interest.

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Author contribution

Authors are equally contributed for the successful research work and writing, editing this manuscript.

List of abbreviations

CA: Cefuroxime axetil

CI: Compressibility index

CP: Cross povidone

DE: Dissolution efficiency

DT: Disintegration time

HLB: Hydrophilic lipophilic balance

HR: Hausner’s ratio

MCC: Microcrystalline cellulose

MDT: Mean dissolution time

PM: Physical mixture

SD: Solid dispersions

SFG: Simulated gastric fluid

WHO: World health organization

REFERENCES

1. Jitender J, Lata B, Sachin K. Formulation and evaluation of solid matrix tablets of repaglinide. Der Pharmacia Sinica, Pelagia Research Library, 2012; 3: 598-603.
2. Mirelabodea, Ioan T, Sorin L, Identification of critical formulation variables for obtaining metoprolol tartrate mini-tablets. Farmacia, 2010; 58: 719-27.
3. Ranjith K, Mahalaxmi R. Pharmaceutical Mini Tablets. Int J Pharm Tech Res, 2014-15; 7: 507-15.
4. Hellebechgaard, Gydahegermannnielsen. Controlled-release multiple-units and single-unit doses a literature review. Drug Dev Ind Pharm, 1978; 4: 53-67.
5. Gross ST, Hoffman A, Donbrow M, Benita S. Fundamentals of the release mechanism interpretation in multiparticulate systems: the prediction of the commonly observed release equations from statistical population models for particle ensembles. Int J Pharm, 1986; 29: 213–22.
6. Mathiowitz, Edith, Ed; Encyclopedia of controlled drug delivery. New York: John Wiley, I, 1999: 9-11.
7. Yuqian D, Zhai Y, Zhang J, Wu C, Luo C, Sun J, et al. Development and evaluation of taste-masked dry suspension of cefuroxime axetil for enhancement of oral bioavailability. Asian J Pharm Sci, 2013; 8: 287-94.
8. Renju P, Janakiraman K, Jyoti H. formulation and evaluation of taste masked oral suspension of cefuroxime axetil using hydroxypropyl-beta-cyclodextrin. Asian J Pharm Clin Res, 2016; 9: 90-2.
9. Shirke SH, Shewale SB, Kulkarni AS, Aloorkar NH. Solid dispersion: a novel approach for poorly water soluble drugs. Int J Curr Pharm Res, 2015; 7: 1-8.
10. Rubendra K, Dinesh KM, Dinesh KJ. Solid dispersion: a novel means of solubility enhancement. J Crit Rev, 2016; 3: 1-8.
11. Gupta MK, Goldman D, Bogner RH, Tseng YC. Enhanced drug dissolution and bulk properties of solid dispersions granulated with a surface adsorbent. Pharm Dev Technol, 2001; 6: 563–72.
12. Takeuchi H, Nagira S, Yamamoto H, Kawashima Y. Solid dispersion particles of amorphous indomethacin with fine porous silica particles by using spray-drying method. Int J Pharm, 2005; 293: 155-64.
13. Rashmi Dahima, Ashish Pachori, Sanjay Netam, formulation and evaluation of mouth dissolving tablet containing amlodipine besylate solid dispersion. Int J Chem Tech Res, 2010; 2: 706-15.

14. Aulton M.E. (Ed.), Pharmaceutics: The science of dosage form design, 2nd Ed. Edinburgh; New York: Churchill Livingstone, 2002; 244: 87–98.
15. Odon P, Kovaci B, Vrecer F, Carvedilol dissolution improvement by preparation of solid dispersion with porous silica, Int J Pharm, 2011; 406: 41-8.
16. Lingam M, Bhasker K, Kalamata VN, Eage CM, Bandari S, Vabalaboina V, et al., Design and evaluation of polymeric coated mini-tablets as multiple unit gastroretentive floating drug delivery systems for furosemide, J Pharm Sci, 2009; 98: 6-7.
17. Sahoo J, Murthy PN, Biswal S, Manik. Formulation of sustained-release dosage form of verapamil hydrochloride by solid dispersion technique using Eudragit RLPO or Kollidon®SR. AAPS Pharm Sci Tech, 2009; 10: 27–33.
18. Khan CA, Rhodes CT. The concept of dissolution efficiency. J Pharm Pharmacol, 1975; 27: 48–9.
19. Arias MJ, Gines JM, Moyano JR, Rabasco AM, dissolution properties and in-vivo behaviour of triamterene in solid dispersions with polyethelene glycols. Pharm Acta Helv 1996; 71: 229-35.
20. Bahl D, Hudak J, Bogner RH. Comparison of the ability of various pharmaceutical silicates to amorphize and enhance dissolution of indomethacin upon co-grinding. Pharm Dev Technol, 2008; 13: 255-69.
21. Rudnic EM, Lausier JM, Chilamkurti RN, Rhodes CT. Studies of the utility of cross linked polyvinylpolypyrrolidine as a tablet disintegrant. Drug Dev Ind Pharm, 1980; 6: 291–309.
22. Shah TJ, Amin AF, Parikh JR, Rajesh H, Parikh RH. Process optimization and characterizations of poloxamer solid dispersions of a poorly water-soluble drug. AAPS Pharm Sci Tech, 2007; 8: E18-E24.