

## Formulation design and evaluation of *Cefuroxime axetil* 125 mg immediate release tablets using different concentration of sodium lauryl sulphate as solubility enhancer

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*Cefuroxime axetil* immediate release tablets were formulated by direct compression method with different percentages of sodium lauryl sulphate (SLS) such as 0.5, 1.0, 1.5 and also without SLS. Resulting batches of tablets were evaluated by both pharmacopeial and non-pharmacopeial methods to ascertain the physico-mechanical properties. Dissolution test were carried out in different medium like 0.07 M HCl, distilled water, 0.1M HCl of pH 1.2 and phosphate buffers at pH 4.5 and 6.8 to observe the drug release against the respective concentration of SLS used. Later, test formulations were compared by *f1* (dissimilarity) and *f2* (similarity) factors using a reference brand of cefuroxime axetil. Significant differences ( $p < 0.05$ ) in dissolution rate were recorded with the change in concentration of SLS in different media. Test formulation T3 containing 1% SLS was found to be best optimized formulation based on assay, disintegration, dissolution and similarity and dissimilarity factors.

**Uniterms:** Cefuroxime axetil/immediate release tablets/physico-mechanical properties. Direct compression. Sodium lauryl sulphate.

Formularam-se comprimidos de liberação imediata à base de cefuroxima axetil, pelo método de compressão direta, com diferentes percentagens de lauril sulfato de sódio (LSS), tais como 0,5, 1,0, 1,5, e também sem SLS. Os lotes resultantes dos comprimidos foram avaliados por ambos os métodos da farmacopeia e não farmacopeicos para determinar as propriedades físico-mecânicas. O teste de dissolução foi realizado em meios diferentes, como HCl 0,07 M, água destilada, HCl 0,1 M com pH 1,2 e os tampões fosfato (pH 4,5 e 6,8) para observar a liberação do fármaco contra a correspondente concentração de LSS utilizado. Em seguida, as formulações de teste foram comparadas por fatores *f1* (dissimilaridade) e *f2* (similaridade), utilizando uma marca de referência de cefuroxima axetil. Diferenças significativas ( $p < 0,05$ ) na taxa de dissolução foram registradas com a mudança na concentração de LSS em diferentes meios de dissolução. A formulação T3 contendo LSS a 1% foi considerada a melhor formulação otimizada com base nos ensaios de desintegração, dissolução e fatores de semelhança e dissimilaridade.

**Unitermos:** Cefuroxima axetil/comprimidos de liberação imediata/propriedades físico-mecânicas. Compressão direta. Lauril sulfato de sódio.

## INTRODUCTION

The solubility of drugs plays a significant role in determining the rate and extent of its absorption, thus finally affecting its bioavailability. Therefore poorly soluble or water insoluble drugs need special consideration

and strategies while designing their solid oral formulations. Rate of drug release from solid oral dosage forms is one of the leading factors, which helps to ascertain the therapeutic efficacy in view of the quantity of drug available for absorption and reaching into blood circulation. Although, the phenomenon is equally applicable and important for all active pharmaceutical ingredient(s) (API), however it is more challenging if the API is antibiotic due to specific action required against microbes.

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Most of the drugs launched in recent years have a poor aqueous solubility. Formulation of poorly water soluble drugs is really a challenge for today's formulation scientists. Their absorption and bioavailability from gastrointestinal tract is greatly influenced by the crystalline state. Due to their variable bioavailability at a given dose, it might be difficult to predict their pharmacology and toxicology (Navnit *et al.*, 2008).

*Cefuroxime* is a second generation cephalosporin antibiotic with a broad spectrum activity and a poor absorption profile from gastrointestinal tract. It led to the synthesis of the 1-acetoxyethyl ester of *cefuroxime* (*cefuroxime axetil*). *Cefuroxime axetil* is a prodrug of *cefuroxime* and is suitable for oral administration. Crystalline *cefuroxime axetil* still does not exhibit adequate bioavailability (<18%) when taken through oral route (Somani, Bhushan, Sen, 2001). It is important that cephalosporin compounds for oral administration should be in a form which provides high bioavailability (90-100%) so that their absorption into the blood stream is maximized and the amount of antibiotic remaining in the gastrointestinal tract is minimized.

According to the Biopharmaceutical Classification System (BCS), *cefuroxime axetil* is a poorly water soluble drug having class II qualities with low solubility but high permeability (Woo, Chang, 2000). Solubility and permeability are the important parameters in formulation development and regulatory standards. For BCS II, the rate limiting step or the slowest step is drug release from the dosage form and solubility in the gastrointestinal fluid and not the absorption; thus by increasing solubility, bioavailability also increases (Ketan, Anuradha, Jignasa, 2012). Solubility of a drug can be enhanced by various means such as solvent deposition, solid dispersion, eutectic mixture, micronization, use of surfactant, molecular encapsulation etc. (Desai, Park, 2004).

The effects of surfactants on the dissolution of drugs have been individually investigated by many researchers for the past several decades. Surfactants act as an absorption enhancer and increase drug dissolution and permeability by promoting wetting and penetration of dissolution fluid into the drug molecules (De Smidt, Grit, Crommelin, 1994). Both ionic and cationic surfactants are effective but anionic surfactants such as sodium lauryl sulphate (SLS) have higher solubility than cationic ones. SLS has been proven as the agent of choice because it is inexpensive and possesses good solubilizing capacity at relatively low concentration. Various studies are available in the open literature that has highlighted the role of SLS as a solubility enhancer (De Smidt, Grit, Crommelin, 1994; Sun, Larive, Southard, 2003).

The aim of present work was to:

1. Formulate *cefuroxime axetil* immediate release tablets by a direct compression method
2. Enhance solubility of *cefuroxime axetil* by using different concentrations of sodium lauryl sulphate
3. Evaluate blends and compressed tablets by both pharmacopeial and non-pharmacopeial methods
4. Study dissolution behavior of test formulations of *cefuroxime axetil* using different media
5. Compare test formulations with a reference brand by one way ANOVA and a model independent approach

## MATERIAL AND METHODS

*Cefuroxime axetil* (CA) USP (Nectar Life Sciences, Ltd. India): 150mg of CA equivalent to 125 mg of *cefuroxime*. Other excipients used were: avicel PH 102® (FMC, USA), starch 1500® (Pregelatinized starch) (Colorcon Ltd., England), sodium lauryl sulphate and magnesium stearate (Fischer, UK). Zinacef® (reference brand) 125 mg film coated tablet (GSK (Pvt) Ltd. Karachi, Pakistan) purchased from the local market. Software used were adds in program DD solver® and Microsoft Excel 2010® for statistical analysis by one way ANOVA.

### Manufacturing of *cefuroxime axetil* tablets

#### *Formulation composition*

Four formulations of *cefuroxime axetil* immediate release tables were designed for direct compression. Compositions were set in such a way that the active ingredient and excipients such as starch 1500 and magnesium stearate remain the same in all the formulations but the concentration of SLS was varied in each formulation and adjusted by avicel PH 102 (Table I). Total compression weight was set at an average weight of 450 mg ( $\pm$  5%).

#### *Blend preparation for compression*

All the ingredients were accurately weighed, sieved manually through a 40 mesh sieve and then mixed in a polyethylene bag for 15 minutes. The mixture was then blended with magnesium stearate for another 5 minutes to get a homogenous blend.

#### *Evaluation of flow properties*

The flowability of the powder blends were evaluated under USP 36/ NF 31, 2013 guidelines as follows,

- Angle of repose ( $\alpha$ )

Angle of repose ( $\alpha$ ) was determined by funnel method. Each blend was poured through a funnel that can be raised vertically until a maximum cone height ( $h$ ) was

**TABLE I** - Composition of *Cefuroxime Axetil* formulations compressed by Direct compression method

Ingredients	T1	T2	T3	T4
	Without SLS (mg/tab)	SLS 0.5% (mg/tab)	SLS 1% (mg/tab)	SLS 1.5% (mg/tab)
<i>Cefuroxime axetil</i>	150.00	150.00	150.00	150.00
Avicel PH 102	259.50	257.25	255.00	252.75
Sodium lauryl sulphate (SLS)	0	2.25	4.50	6.75
Starch 1500	31.50	31.50	31.50	31.50
Magnesium stearate	9.00	9.00	9.00	9.00
Total compression weight	450.00	450.00	450.00	450.00

T1= Test formulation one, T2= Test formulation two, T3= Test formulation three, T4= Test formulation four

achieved. The radius of the heap ( $r$ ) was measured and angle of repose calculated as,

$$\alpha = \tan^{-1} (h/r)$$

- Bulk density ( $\rho_b$ )

Apparent bulk density ( $\rho_b$ ) was determined by introducing perceived blend of test formulations in to a graduated cylinder and measuring the weight ( $M$ ) and bulk volume ( $V_b$ ) using the formula,

$$\rho_b = M/V_b$$

- Tapped density ( $\rho_t$ )

Tapped density ( $\rho_t$ ) was determined by tapping the known mass of a blend in a measuring cylinder for a fixed time. The minimum volume ( $V_t$ ) occupied in the cylinder and weight ( $M$ ) was measured and the tapped density calculated as,

$$\rho_t = M/ V_t$$

- Compressibility Index

Powder compressibility is a more significant way to measure free flow properties is the ease by which a material can be persuade to flow and is calculated by % compressibility as follows:

$$C = (\rho_t - \rho_b) / \rho_t * 100$$

- Hausner's ratio

Hausner's ratio is an index of ease of powder flow and determined by following formula,

$$\text{Hausner's ratio} = \rho_t/\rho_b$$

#### Tablet compression

Powder blends were compressed on a single punch machine (Korsch, Erweka, Germany) fitted with a convex shaped punch having a diameter of 12.38mm to get oval tablets each weighing 450mg ( $\pm 5\%$ ). Hardness set for compression ranged between 6-7 kg. A minimum of fifty

tablets were compressed for each batch on separate days at room temperature.

#### Tablets testing

The quality parameters of finished tablets were evaluated by USP 36/ NF 31, 2013 guidelines and non-pharmacopeial methods as stated below.

#### Weight variation

The variation of the weight of individual tablets is an apparent indication of the corresponding variation in the drug content (Rawlins, 1995). The weight variation evaluation of test formulations and reference brand were carried out by individually weighing 20 tablets on a Type 1 balance (Sartorius GmbH; type A 6801) and then mean weight and standard deviation were calculated.

#### Tablet thickness and diameter

The thickness of a tablet was the result of the amount of fill permitted to enter the die and the amount of pressure applied during compression (Allen, Popvich, Ancel, 2011). Diameter and thickness of 20 tablets, each of the innovator and test formulations, were determined by a vernier caliper in mm (CD-6, CSX, Mitutoyo, Japan).

#### Tablet hardness

To determine crushing strength, hardness of randomly selected 20 tablets of test formulations was determined in kg using a Hardness Tester (Fujiwara, Seisukusho Corporation, Japan).

#### Friability testing

Friability test was performed on 20 randomly selected tablets of each test formulations. Tablets were cleared from any loose dust by a soft brush and weighed accurately. Each set of tablets were placed separately in a friabilator (H.Jurgens and Co-GmbH, D2800, Germany)

and run for 4 minutes (25 rpm). At the end of the test, tablets were removed, cleared from any loose dusts, observed for any capping and then their final weight was determined to calculate the loss of weight in percent.

#### Disintegration

The disintegration test was ensuring the dispensability of tablet content in purified water at a  $37 \pm 0.5$  °C temperature within appropriate time (Allen, Popvich, Ancel, 2011). Disintegration of compressed tablets and innovator was performed by placing each tablet in a tube of basket rack assembly of disintegration apparatus (Erweka, ZT2, Heusenstamm Germany).

#### Assay test method

The test formulations and innovator were assayed by high performance liquid chromatography method (HPLC) as per USP 36/ NF 31, 2013 guidelines. The suitably filtered and degassed mixture of mobile phase composed of 0.2 M Monobasic ammonium phosphate and methanol (620:380) with a flow rate of 1.5 mL per minute. The liquid chromatography is equipped with a 278-nm detector (UV detector SPD 10-AVP, Shimadzu Corp., Tokyo, Japan), a pump LC-10 ADVP, Communication Bus Module CBM 102 and separation of drug was done by Promosil® (Agela Technologies, USA) C-18, 4.6 x 250-mm column containing 5µm packing with injection volume about 10µL.

For assay preparation twenty tablets were accurately weighed and crushed in a porcelain mortar. Powder equivalent to 2 mg of *Cefuroxime* per mL transferred with the aid of methanol to a such capacity of volumetric flask and shaken by mechanical means for about 10 minutes. It was then diluted with methanol to a volume and filtered a portion of this stock mixture by Whatman® filter paper no. 41. From this solution, 5 mL was promptly transferred to 50 mL volumetric flask. This was followed by the addition of 5 mL of internal standard (Acetanilide in methanol containing 5.4 mg/mL), 8.8 mL of methanol and then diluted with 0.2M Monobasic ammonium phosphate to 50 mL. The solution was filtered through 0.45 µm Millipore® filter and injected in to the column, same procedure were carried out for reference standard solution of *Cefuroxime axetil*. The drug content was measured and calculated. The assay test method was carried out in triplicate.

#### In vitro dissolution studies

The dissolution studies of the compressed test tablets and reference brand were carried out as per USP 36/ NF 31, 2013 guidelines by using a USP apparatus II (Erweka DT, Heusenstamm, Germany). Dissolution

was performed in 900 ml of 0.07M HCl at  $37 \pm 0.5$  °C at 100 rpm. An aliquot of 10 mL of solvent was taken out from vessels at 5, 10, 15, 20, 25, 30, 45, 60, 90 and 120 minutes and volume was compensated by fresh medium. Drug concentration was calculated by UV-Vis spectrophotometer 1800 (Shimadzu, Kyoto, Japan) at 278 nm with dissolution medium taken as blank. The dissolution profile was also established in distilled water, 0.1 M HCl of pH 1.2 and phosphate buffers at pH 4.5, 6.8 using the same sampling times as described above to evaluate the release of drug in the new formulations. Each experiment was repeated in triplicate.

## RESULTS AND DISCUSSION

The solubility and dissolution factor of poorly soluble drugs in gastrointestinal fluid after oral administration is not only of great importance but also challenging at the same time. Therefore, such drugs require to be available in aqueous solution form at the absorption site. Further, due to the solubility factor, the poorly water soluble drugs usually need high dose in order to attain reasonable plasma peak concentration to achieve the desired therapeutic effect after oral administration. Apparently, this is not a good idea to proceed and formulate an oral dosage formulation of poorly soluble or insoluble drugs with this approach because this is very much likely to produce insufficient bio-availability, thus affecting therapeutic response. The partition coefficient of an active pharmaceutical ingredient(s) (API) does play a very important role in knowing its solubility or alternatively, the hydrophilicity or hydrophobicity of that API. In the present study as the drug chosen is *cefuroxime axetil* which is classified under class II of BCS (low solubility and high permeability), therefore considerable attention has been focused to design a suitable formulation which can increase its bioavailability and at the same time convenient in manufacturing, cost effective and reproducible.

*Cefuroxime axetil (CA)* is a prodrug which is hydrolyzed by esterase of the gut mucosa, releasing the active cefuroxime base. It has *in-vitro* microbial activity similar as the parent cefuroxime. The bioavailability and pharmacokinetics of the drug has been observed to vary depending on the physical form and having more stability in dosage forms (Perry, Brogden, 1996). Several reports confirm that the bioavailability can be improved by using different solubilizers and hence improving the solubility and permeability issues of the drug (Somani, Sethi, Tyagi, 2003). In the present study, *cefuroxime axetil* immediate release tablets were formulated with different concentrations of sodium lauryl sulphate (Table I).

The direct compression (DC) method was selected for manufacturing. Direct compression method is more convenient, economical and increases the stability of active ingredients by reducing detrimental effects (Shangraw *et al.*, 1988). This method was also successfully used by Nanjwade *et al.* in making immediate release *cefuroxime axetil* tablets (Nanjwade *et al.*, 2010).

Micromeritic evaluation of all formulation blends (T1-T4) revealed that angle of repose, bulk density, tapped density, Hausner's ratio and compressibility index, was within the limits as specified by USP 36/ NF 31, 2013. Test three (T3) blend showed excellent flow while test one (T1), test two (T2) and test four (T4) showed a good flow (Table II). Good flow of the blends might be due to appropriate composition of avicel PH 102 and magnesium stearate in all formulations (Lahdenpaa, Niskanen, Yliruusi, 1997).

After ascertaining flowability, blends were compressed on single punch machine and the compressed tablets were evaluated for pharmaceutical attributes.

Tablets were easily compressed and found to be free from any compression defects such as breaking, sticking and lamination. Weight variation was easily monitored within the prescribed limits as specified by USP 36/ NF 31, 2013 guidelines while the thickness ranged within  $\pm 5\%$ . The hardness of all formulations was found to be 6.23 to 7.02 kg. T1, T3 and T4 showed almost same hardness (6.83, 6.23 and 6.42 kg respectively) while T2 showed highest hardness (7.02 kg). For a satisfactory tablet, hardness of 5 kg is usually considered suitable and is used as a guide in compression. When the tablets were subjected to friability testing, results were found to be within the acceptable limits (0.31 to 0.57%). It directly relates to the tablet hardness and strength which is in proportion to the composition of the formulation (Table III). Zhang *et al.*, in 2003, reported the physical properties of commonly used direct compression binder and explained the effect of avicel PH 102 and starch on tablet dosage forms (Zhang, Law, Chakrabarti, 2003).

The conventional immediate release oral solid dosage forms need to be disintegrated from its intact

**TABLE II** - Flow properties of *Cefuroxime axetil* 125 mg directly compressible blends

Test Formulation	Mass (g)	Bulk Volume (mL)	Tapped Volume (mL)	Bulk Density (g/mL)	Tapped Density (g/mL)	Angle of Repose ( $\theta^\circ$ )	Compressibility Index (%)	Hausner Ratio -
T1	8.05 $\pm$ 0.05	9.85 $\pm$ 0.06	8.65 $\pm$ 0.07	0.81 $\pm$ 0.03	0.93 $\pm$ 0.12	33.20 $\pm$ 0.06	12.90 $\pm$ 0.05	1.14 $\pm$ 0.01
T2	9.38 $\pm$ 0.09	10.35 $\pm$ 0.10	9.10 $\pm$ 0.15	0.90 $\pm$ 0.01	1.03 $\pm$ 0.05	31.26 $\pm$ 0.05	12.62 $\pm$ 0.04	1.14 $\pm$ 0.02
T3	8.50 $\pm$ 0.15	10.10 $\pm$ 0.12	9.15 $\pm$ 0.05	0.84 $\pm$ 0.02	0.92 $\pm$ 0.11	28.88 $\pm$ 0.04	8.69 $\pm$ 0.03	1.09 $\pm$ 0.01
T4	9.54 $\pm$ 0.03	10.40 $\pm$ 0.05	9.15 $\pm$ 0.01	0.91 $\pm$ 0.01	1.04 $\pm$ 0.06	33.69 $\pm$ 0.06	12.50 $\pm$ 0.05	1.14 $\pm$ 0.02

T1= Test formulation one, T2= Test formulation two, T3= Test formulation three, T4= Test formulation four. Each value is a Mean $\pm$ SD of three determinations

**TABLE III** - Pharmaceutical characteristics of reference and compressed formulations of *Cefuroxime axetil*

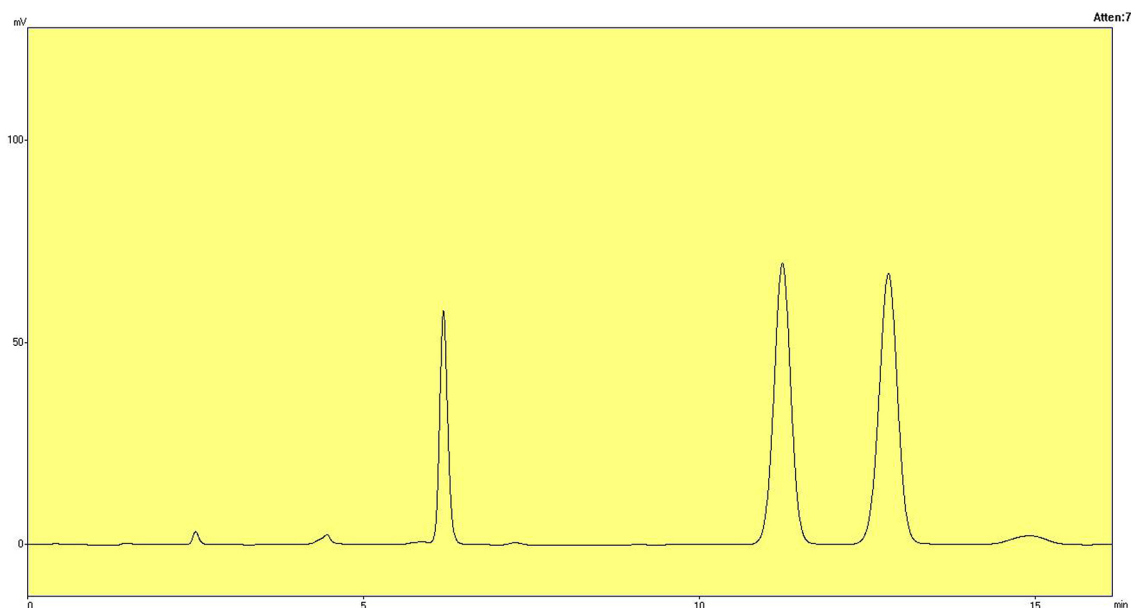
Test Formulation	Wt. Variation (Mean $\pm$ S.D) (mg)	Thickness (Mean $\pm$ S.D) (mm)	Diameter (Mean $\pm$ S.D) (mm)	Hardness (Mean $\pm$ S.D) (kg)	Friability (Mean $\pm$ S.D) (%)	Disintegration Time (Mean $\pm$ S.D) (Seconds)	Assay HPLC (Mean $\pm$ S.D) (%)
<b>Pharmacopoeial Limits (USP 32/ NF 27)</b>	$\pm 5\%$	$\pm 5\%$	-	At least 5 kg	NMT 1%	NMT 15 min.	90-110%
A1 Ref.	227.10 $\pm$ 1.16	3.43 $\pm$ 0.04	12.04 $\pm$ 0.20	NA	NA	47.33 $\pm$ 0.58	98.84 $\pm$ 0.29
T1	450.00 $\pm$ 4.23	4.10 $\pm$ 0.05	12.38 $\pm$ 0.04	6.83 $\pm$ 0.91	0.57 $\pm$ 0.12	61.33 $\pm$ 3.06	93.58 $\pm$ 0.73
T2	450.45 $\pm$ 3.70	4.11 $\pm$ 0.05	12.38 $\pm$ 0.05	7.02 $\pm$ 0.95	0.37 $\pm$ 0.10	59.00 $\pm$ 1.00	94.94 $\pm$ 0.99
T3	450.31 $\pm$ 3.51	4.08 $\pm$ 0.03	12.37 $\pm$ 0.04	6.23 $\pm$ 0.38	0.31 $\pm$ 0.14	51.33 $\pm$ 0.58	101.43 $\pm$ 0.79
T4	449.86 $\pm$ 3.71	4.10 $\pm$ 0.04	12.38 $\pm$ 0.04	6.42 $\pm$ 0.63	0.41 $\pm$ 0.13	54.00 $\pm$ 1.00	101.85 $\pm$ 0.41

A1 Ref = Ref. coated brand of GSK, Pakistan., T1= Test formulation one, T2= Test formulation two, T3= Test formulation three, T4= Test formulation four, NA= not applicable

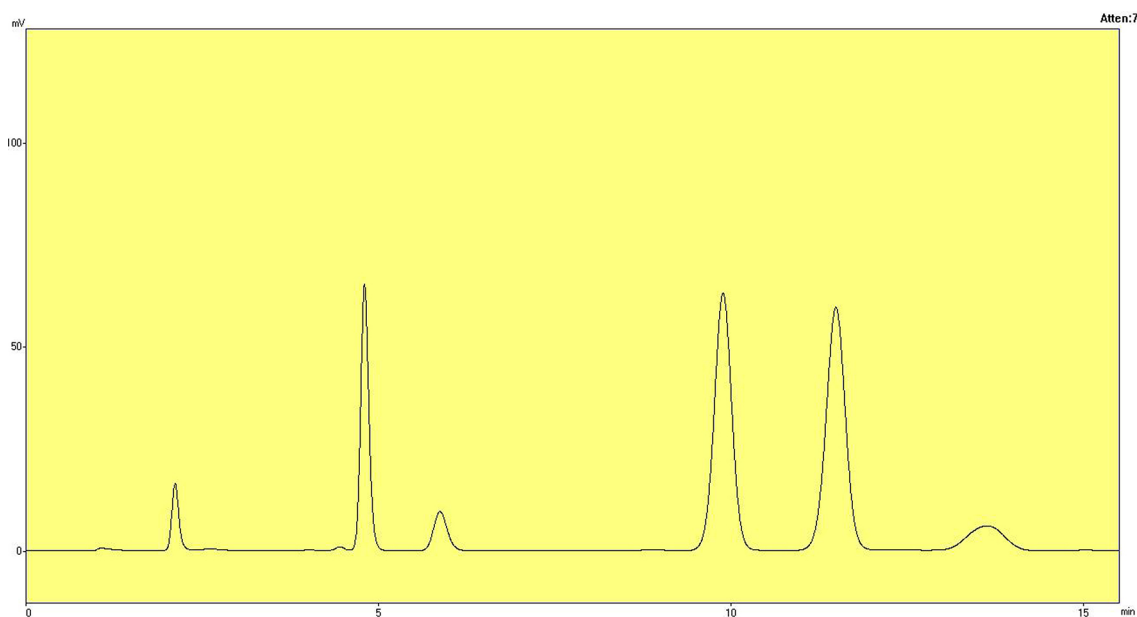
form and get dissolved to show its release pattern. Thus the inclusion of the right disintegrant is a prerequisite for optimal bioavailability (Bhowmik *et al.*, 2010). In the present study, all the test formulations were disintegrated quickly within one minute and were in compliance with USP guidelines. Starch 1500 (pregelatinized starch) is widely used as a disintegrant in tablet manufacturing and in one study, formulation of lamivudine tablets with starch 1500 exceeded the disintegration and dissolution performance (Rahman *et al.*, 2008).

Pharmaceutical assay was performed by high performance liquid chromatography method (HPLC). Assay results for test and reference formulations were within USP 36/ NF 31, 2013 limits (90-110%). This indicates that the blending time selected for test formulations was appropriate and resulted in a uniform random blend (Table III and Figure 1, 2).

The multiple point dissolution studies of *cefuroxime axetil* tablets were performed in five different dissolution medium i.e., 0.07 M HCl (USP dissolution medium),



**FIGURE 1** - HPLC Chromatogram of standard solution containing internal standard, acetanilide (6.18 min), cefuroxime axetil diastereoisomer B (11.23 min) and cefuroxime axetil diastereoisomer A (12.83 min).



**FIGURE 2** - HPLC Chromatogram of test formulation T3 solution containing internal standard, acetanilide (4.80 min), cefuroxime axetil diastereoisomer B (9.88 min) and cefuroxime axetil diastereoisomer A (11.49 min).

0.1 M HCl of pH 1.2, phosphate buffers (pH 4.5 and 6.8) and distilled water. In test formulation one (T1), which was formulated without SLS, less drug released was observed in 0.07 M, 0.1 M HCl, and phosphate buffers pH 4.5 and 6.8 (range:  $60.34 \pm 0.87$  -  $70.35 \pm 1.35$ ) but more than 80% ( $81.33 \pm 1.14$ ) drug was released in water in one hour. In case of test formulation two (T2) which was formulated with 0.5% of SLS, lowest drug release was found in 0.1 M HCl ( $36.59 \pm 0.86$ ) while almost same drug release were detected in other tested medium in one hour sampling time (range:  $72.31 \pm 1.08$  -  $82.52 \pm 1.56$ ). Dissolution results of test formulation three (T3) was very promising which was formulated with 1% SLS. Highest drug release was

found in phosphate buffer pH 4.5 ( $91.81 \pm 0.60$ ) while all the other tested medium showed more than 80% (range:  $82.34 \pm 0.61$  -  $84.12 \pm 1.10$ ) drug release within one hour. Likewise T1 and T2, test formulation four (T4) which was formulated with 1.5% SLS also showed somewhat lower release rates in 0.07 M HCl ( $63.46 \pm 1.19$ ) but more promising release rate in 0.1 M HCl ( $77.59 \pm 1.85$ ) within one hour of dissolution testing. In other medium, T4 showed highest release pattern in pH 6.8 phosphate buffer followed by 4.5 phosphate buffer and distilled water (Figure 3, 4, 5, 6 and 7).

When results were subjected to statistical analysis by one way ANOVA, revealed a significant difference

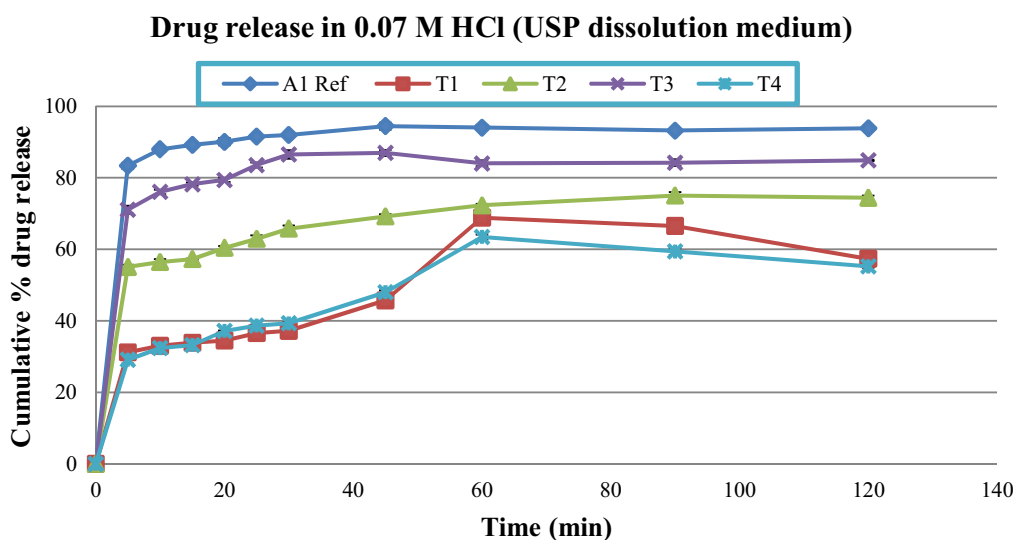


FIGURE 3 - Released pattern of Reference and test formulations in 0.07 M HCl dissolution medium (Mean±SD).

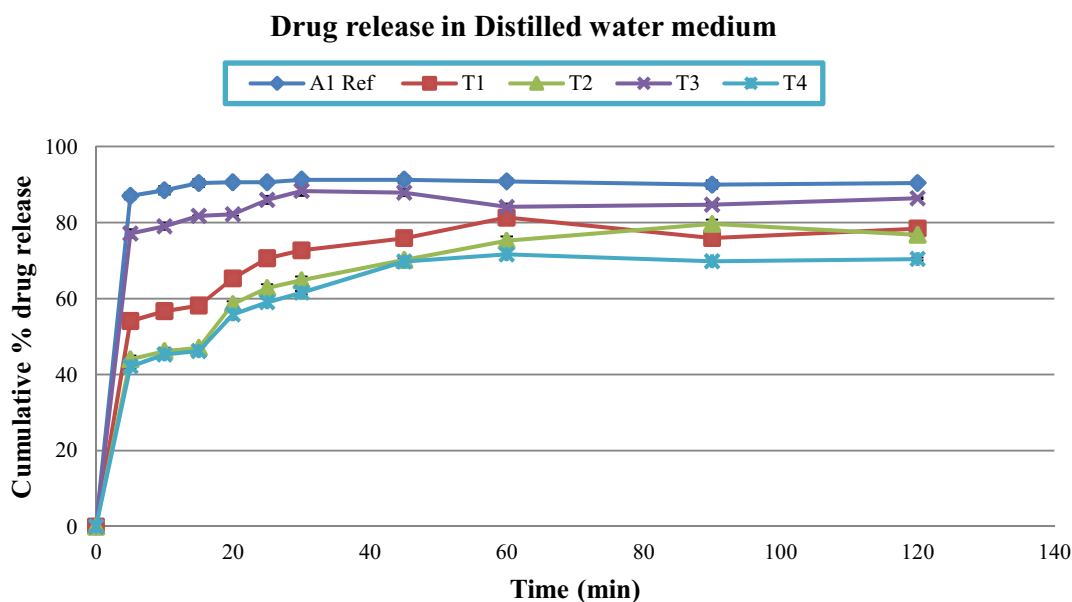


FIGURE 4 - Released pattern of Reference and test formulations in distilled water dissolution medium (Mean±SD).

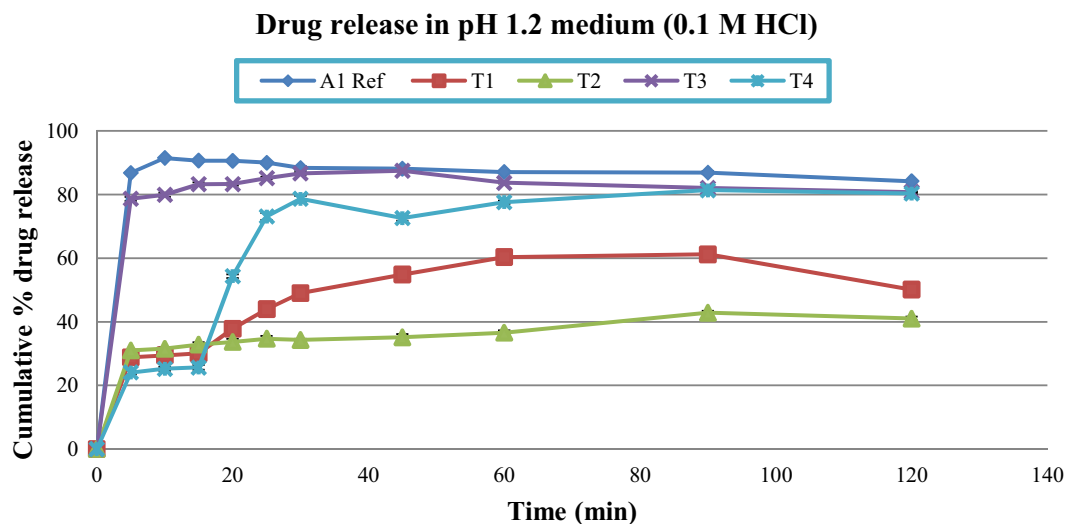


FIGURE 5 - Released pattern of Reference and test formulations in pH 1.2 (0.1 M HCl) dissolution medium (Mean±SD).

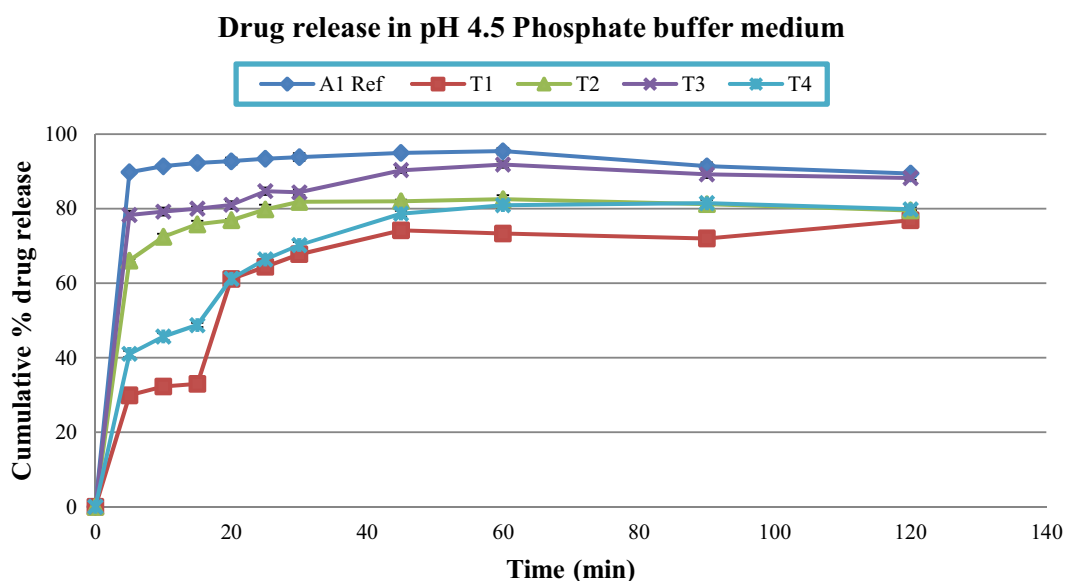


FIGURE 6 - Released pattern of Reference and test formulations in pH 4.5 (Phosphate Buffer) dissolution medium (Mean±SD).

( $p < 0.05$ ) among reference and test formulation (T1-T4) in all dissolution medium at each sampling time, except in test formulation three (T3) in 0.1 M HCl a non-significant difference ( $p > 0.05$ ) were observed at 45 minutes time interval. This result indicates the role of sodium lauryl sulphate as a solubility enhancing agent for poorly water soluble drugs. It also revealed that 1% SLS is appropriate for enhancing solubility of *cefuroxime axetil* tablets, which is in line with Muhammad *et al.* (2012) studies conducted recently in the same dissolution medium. It appears that in the present study, SLS due to its anionic nature favors maximum micelle formation at 1% concentration and thus increases the dissolution rate of *cefuroxime axetil*. Use of SLS from 0.5-2% was also recommended by the

FDA for poorly soluble drugs (Chilukuri, Sunkara, Young, 2007). Razzka *et al.* (2012), studied the effect of different concentrations of SLS on the release of carbamazepine matrix tablets and reported promising results. In another study Jinno *et al.* (2000) also reported effect of surfactants on the dissolution profile of poorly water soluble weakly acidic drugs and reported SLS as the best choice for micelle formation and solubility enhancement.

A model independent approach as recommended by Moore and Flenner (1996) that comprises of calculating a dissimilarity factor ( $f1$ ) and a similarity ( $f2$ ) factor were also done to compare an innovator brand with the test formulations. It is reported in the previous works that the dissolution and pH solubility outcomes of both



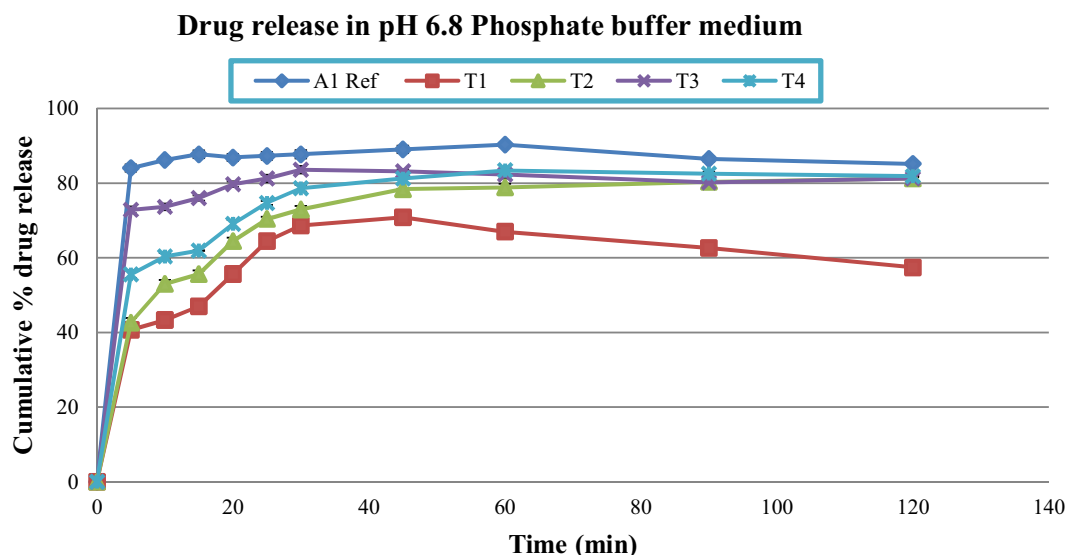


FIGURE 7 - Released pattern of Reference and test formulations in pH 6.8 (Phosphate buffer) dissolution medium (Mean $\pm$ SD).

TABLE IV - Difference factor ( $f_1$ ) and similarity factor ( $f_2$ ) of all formulation with Reference at different pH

S. No	Formulations comparison	Factor	0.07 M HCl (D.M)	Distilled water	pH 1.2 (0.01M HCl)	pH 4.5 Phosphate buffer	pH 6.8 Phosphate buffer
1.	A1 Ref. vsT1	$f_1$	51.12	23.53	49.61	36.74	33.67
		$f_2$	15.96	32.09	16.94	20.91	25.59
2.	A1 Ref. vsT2	$f_1$	28.69	30.63	60.02	15.86	22.14
		$f_2$	28.81	26.11	13.64	40.85	32.19
3.	A1 Ref. vsT3	$f_1$	10.43	7.04	6.02	8.40	8.83
		$f_2$	50.54	58.10	60.18	52.60	54.04
4.	A1 Ref. vsT4	$f_1$	52.09	34.35	32.95	29.26	16.24
		$f_2$	15.82	24.38	20.86	25.76	36.65

drugs and prodrugs could be relevant and the FDA and ICH recommends  $f_1$  and  $f_2$  factors for the comparison of dissolution profiles (FDA, 1997; 2003). Dissolution curves considered to be equivalent if  $f_1$  ranges from 1-15 and  $f_2$  ranges from 50-100. Test formulation three (T3) showed a smallest differential values for  $f_1$  (10.43, 7.04, 6.02, 8.40, 8.83) and a good similarity values for  $f_2$  (50.54, 58.10, 60.18, 52.60, 54.04) in dissolution media (Table IV). Previously for *cefuroxime axetil*, similar finding have been reported by Iyad *et al.* who used model independent approach using  $f_2$  factor only (Muhammad *et al.*, 2012).

## CONCLUSION

*Cefuroxime axetil* 125 mg tablets were successfully formulated by direct compression method. Likewise previous studies, incorporation of sodium lauryl sulphate

in the present study was found to be beneficial in enhancing solubility of poorly soluble drugs. Dissolution rate of *Cefuroxime axetil* was studied in various medium including USP dissolution medium that gave a chance to compare its release rate in various media and to select the best medium for this drug. Use of  $f_1$  and  $f_2$  further give an insight about the *in-vitro* performance of *Cefuroxime axetil*. Further studies using other surfactants or other approaches for enhancing solubility are recommended for future workers.

## ACKNOWLEDGEMENTS

The Principal author is very grateful to Mr. Riaz of Opal Laboratories (pvt) Ltd. for providing active raw material of *Cefuroxime axetil* USP for the research project. The part of the data has been presented in poster

publication at Second National Conference on Pharmacy Research held in Dow College of Pharmacy, DUHS (Ojha campus), Karachi, Pakistan dated 7<sup>th</sup>, September 2013.

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Received for publication on 29<sup>th</sup> December 2013

Accepted for publication on 23<sup>rd</sup> March 2014

