Research Article

Formulation and Evaluation of Amoxycillin and Potassium Clavulanate Bilayered Tablets

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ABSTRACT

In the present study bilayered tablets were prepared to separate the amoxycillin & potassium clavulanate layer. Since, there are wide variabilities in the quality of solid dosage forms, especially in their dissolution and pharmacokinetics profile due to physicochemical interactions. Amoxycillin trihydrate & potassium clavulanate have similar structures. The similarities of their molecular & crystal structures suggest an increase likelihood of interaction between the two compounds. In addition, the two compounds having a big difference in pKa, which makes the mixture prone to chemical acid-base reaction. Thus, in order to increase the stability of the dosage form bilayered tablets were prepared. Potassium clavulanate is highly water soluble while amoxycillin is less water soluble thus, binder was added to layer containing potassium clavulanate and disintegrant was added to layer containing amoxycillin so that the realease of drugs occur at the same time from both the layer. The tablet was prepared by dry granulation method.

The prepared batches of tablets were evaluated for thickness, hardness, friability, weight variation, drug content, disintegration time, dissolution studies & stability studies.

Keywords: Amoxycillin, potassium clavulanate, bilayered tablets, direct compression.

INTRODUCTION

Bilayer tablet is new era for the successful development of solid oral dosage form along with various features to provide a way of successful drug delivery system[11]. The term Bi-layered tablet refers to tablet containing two subunits that may contain same or two to three different drugs. Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose[6].

At most care has to be taken during bilayer tablet formulation to overcome common bi-layer problems, such as layer separation, insufficient hardness, inaccurate individual layer weight control, cross-contamination between the layers, reduced yield, etc[4].

The oral bioavailability of drug is dependent on disintegration, dissolution and various physiological factors. In recent years, scientists have focused their attention on the formulation of quickly disintegrating tablets by using suitable diluents and super disintegrants[3].

Amoxycillin and Potassium Clavulanate have similar structure. The similarities of their molecular and crystal structure suggest an increased likelihood of interaction between the two compounds resulting in physicochemical interactions. In addition, the two compounds have a big difference in pKa, which makes the mixture more prone to chemical acid-base reaction. Bilayered tablets were prepared to separate the Amoxycillin and Potassium Clavulanate layer thus, in order to increase the stability of the dosage form[5].

Amoxycillin exerts a bactericidal action against sensitive organisms during the stage of active multiplication through the inhibition of the biosynthesis of bacterial cell wall mucopeptides. Clavulanic acid inhibits specific β-lactamases of some microorganisms and allows amoxycillin to inhibit amoxycillin (ampicillin) resistant organisms which produce clavulanic acid sensitive β-lactamases[1].

Clavulanic acid is a β-lactam structurally related to the penicillins and possesses the ability to inactivate a wide variety of β-lactamases by blocking the active sites of these enzymes. Combination of amoxycillin and clavulanate potassium may prevent amoxycillin from hydrolyzed by β-lactamase[1].

Amoxicillin and clavulanate potassium are well absorbed from the gastrointestinal tract after oral administration.

People with hypersensitivities (allergies) to penicillins or beta-lactam antibiotics, such as cephalosporins, should not handle the amoxicillin/clavulanate as allergic reactions could occur just from contact.

MATERIALS AND METHODS

(a)Materials

Amoxycillin Trihydrate & Potassium Clavulanate was produced from DSM Sinochem Pharma, Microcrystalline cellulose from Mingtai chem. Cells co. Ltd., Cross Povidone from Base Chemicals, Magnesium Stearate from Suzong Chemicals, Sunset Yellow Supra from Biocon Ltd and Aerosil from Wacker.

Dosage form: Eight formulations of Amoxycillin and Potassium Clavulanate (625 mg) bilayered tablets were prepared (Table 3). It was coded as F1-F8 and single layered marketed Amoxycillin and Potassium Clavulanate tablets were purchased from pharmacy shop. And both the bilayered tablets and marketed single layered tablets are stored properly for further evaluations.

Solvents and reagents: Methanol For HPLC, Water was double distilled.

(b)Method

1. **Preformulation Study**
2. **Dry Granulation**
3. **Pre-compression Studies**
4. **Post-compression Studies**

- **Pre-formulation Study**

Identification of Amoxycillin & Potassium Clavulanate By HPLC

Identification of Amoxycillin & Potassium Clavulanate were Performed by HPLC. According to Indian Pharmacopoeia if the retention times of standard and test product are same then they are said to be similar products.

(a) Methodology & Procedure

for identification of APIs, mobile phase was prepared by dissolving 7.8 gm disodium hydrogen Ortho Phosphate in 1000ml of water, then 50ml of methanol was mixed in 950ml of this solution. The flow rate of mobile phase was 1.5 ml/ min, sample injected volume was 20µl, and standard and test was prepared with the concentration of 100 mg in 100 ml water. The column used was of C-18 type. HPLC column was firstly washed with hot water and then with mobile phase for removing the previous solvents, then the column was saturated to obtain the base line after that one trail was taken to check retention time then the standard and test product were analysed.

- **Dry granulation**

Raw material➔ weighing➔ screening➔ mixing➔ slugging➔ milling➔ screening➔ mixing➔ compression**.**

Procedure

The first step of formulation of Amoxycillin and Potassium Clavulanate bilayered tablet was sifting (Table 1). Then in 2nd step of dry blending, the sifted material of step first was loaded in the Octagonal blender & mixed for 15 minutes. Then, it is compacted by Roll compactor at the temperature of 23-25C. Then the compacted material was passed through Oscillatory Granulator through 2.5 mm screen. Then the milled material of previous step was passed through 18 # S.S. mesh. After sifting the granular powder was dried in Vacuum Tray Dryer for Two hours at 60^0C temperature and vacuum at 710 ± 10 mm Hg. Then Potassium Clavulanate was sifted through sifter fitted with sieve # 30. After Sifting the Drying material was loaded in the Octagonal blender and Potassium Clavulanate, Aerosil & Magnesium Stearate was added and mixed for 30 minutes. After that final step was compression of tablet, 27 stations D tooling machine was used to compress Amoxycillin & Potassium Clavulanate bilayered tablet.

- **Pre Compression Studies (Evaluation of granules)**

(a) Bulk density

Apparent bulk density was determined by placing pre-sieved drug excipient blend in to a graduated cylinder and measuring the volume and weight as it is. Bulk density was determined by using following formula[2].

Bulk Density = Mass / Volume

(b) Tapped density

Weighed sample of powder mixture was transferred to a graduated cylinder and was tapped for a fixed time for a fixed number of taps (100). The tapped density was determined by using the following formula[2].

$$\text{Tapped Density} = \frac{\text{Weight of powder taken}}{\text{Tapped Volume}}$$

(c) Carr's index

Based on the apparent bulk density and the tapped density, the percentage compressibility of the powder mixture was determined by the following formula[2].

$$\text{Carr's Index}(\%) = \frac{(\text{Tapped Density} - \text{Bulk Density})}{\text{Tapped Density}} \times 100$$

(d) Hausner's Ratio

It is an indirect index of ease of measuring the powder flow[2]. It is related to interparticle friction. It is calculated by the following formula[2].

$$\text{Hausner's Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

(e) Angle of repose: Angle of repose is determined experimentally by allowing a sample to flow onto a flat surface, and then measuring the angle with respect to horizontal[7]. Angle of repose of a bulk solid can be described using the following equation[8].

$$\tan \alpha = h / r$$

where, α - measure of angle formed by heap to the horizontal surface,
h - height of heap,
r - radius of heap.

Post Compression Studies (*Evaluation of tablets)*

(a) Tablet Thickness

Ten tablets were picked randomly from each batch and each tablet was placed in between, spindle OF Vernier Caliper and the thickness reading was obtained in millimeters[9].

(b) Tablet Hardness

The tablet was held between a fixed anvil and a moving jaw and the load gradually was increased until the tablet just fractured. The value of load at this point gives a measure of the tablet hardness. For each batch the average hardness was obtained from the individual hardness of four tablets[9].

(c) Friability

Tablet friability is evaluated by using Roche Friabilator[10]. Ten tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution[6,11]. After 4 min, the tablets were weighed and the percentage loss in tablet weight was determined[6,11]. The tablets that lose less than 0.5 to 1% of tablet weigh were considered acceptable[14].

Percentage of Friability

$$\frac{\text{Initial Weight} - \text{Final Weight}}{\text{Initial Weight}} \times 100$$

(d) Weight Variation Test

Twenty tablets from each batch of formulation were selected at random and weighed individually[9] and the average weight was also calculated[6,11].

(e) Disintegration Time

The test was performed using Disintegration test apparatus having six glass tubes that were 3inches long, open at the top, and held against 10" screen at the bottom end. The temperature of distilled water was maintained at 37°C. The time taken for the last tablet or its fragment to pass through the mesh into the disintegration medium was recorded[9].

(f) Drug Content

20 tablets were taken and powdered. A quantity of powder equivalent to its average weight was taken and dissolved in water and is then assayed by HPLC for determination of drug content[15].

(g) Dissolution Studies

The release of Amoxycillin & Potassium Clavulanate from Bilayered tablets was determined by using Dissolution type II test apparatus. The dissolution test was performed using 900 ml water at 37 ± 0.5C temperature and at 75rpm. At specified time intervals, samples of 5 ml were withdrawn from the dissolution medium and that amount was replaced with fresh medium to maintain the volume constant. The samples were filtered and the percent of drug dissolved was determined by analyzing the sample through HPLC[15].

(h) Stability Studies

F8 was packed in suitable packaging and stored under the following conditions for a period as prescribed by ICH guidelines for accelerated studies[12]. The tablets were withdrawn and analyzed for physical characterization (Visual defects), Average Thickness, Weight Variation, Hardness, Friability, Disintegration Time, Dissolution and drug content[12,13] (Table 6&7).

RESULTS

Preformulation study

Solubility, assay of Active pharmaceutical ingredients was determined by HPLC and flow properties of granules were also determined.

Solubility

Amoxycillin was slightly soluble in water, methanol and ethanol and Potassium Clavulanate was freely soluble in water and methanol.

Identification

It was performed by HPLC. The retention time of Standard curve and test curve were same. RT of standard Amoxycillin was 2.060 and RT of test was also 2.06 (Fig.1&2), RT of standard Potassium Clavulanate was 1.924 and RT of test was also 1.928 (Fig.3&4), The RT of mixture of Amoxycillin & Potassium Clavulanate standard was 4.082 & 2.143 and RT of test was 4.082 & 2.143 (Fig.5&6).

Flow Properties

Carr's index of all batches was 8 to 14 it was in the limit and the Hausner's ratio was also in limit, i.e. 1.05-1.25.Angle of repose was also successfully determined, it was 20- 25 (Table 2), thus the granules were having good flow property .

Evaluation of tablets

Tablets were evaluated for weight variation, hardness, friability, Disintegration time, and Equivalent Relative Humidity, Assay and dissolution study (Table 4). Tablets were having uniform weight, hardness and friability data indicated good mechanical resistance of the tablets. First the tablets were evaluated for average weight; the tablets show values between 1020 mg to 1040 mg. The tablets were evaluated for length, thickness and width and it was found to be within the limits. Lengths of all batches were found from 19.2 to 19.3, Thickness was from 6.7 to 6.9, widths of all batches were 9.0 to 9.2. Disintegration time was found in between the 6.56 to 7.58mins. The Batch F8 shows best disintegration time it was 6.56 min (Fig.9). The %ERH of tablets was also determined, it was within the limit (0.05 to 0.07).

The % releases of batch F1-F4 were 83%-90% and from batch F5-F8 was within the limit of 93-100%. Batch F8 shows best release. Batch F8 shows 99.09% Amoxycillin (Fig.7) & 99.18% of Potassium Clavulanate (Table 5, Fig.8) release.

Bilayered Tablets were found to be more stable than the marketed preparation of single layered amoxycillin and potassium clavulanate tablets (Table 6&7).

CONCLUSION

It was concluded that Amoxycillin & Potassium Clavulanate bilayered tablet can be formulated which was found to be more stable than single layered amoxycillin and potassium clavulanate tablets thus, shelf life of Amoxycillin and potassium clavulanate tablet can be improved by increasing the stability of product by developing bilayered tablet.

The % release of amoxycillin and potassium clavulanate was maintained from both the layers using various concentration of disintegrant and binder in first and second layer respectively.

The % release of batch F8 was found to be best i.e., 99.09% Amoxycillin & 99.18% of Potassium Clavulanate was released in 30mins (Table 5, Fig.7&8).

ACKNOWLEDGEMENT

I express my heartfelt thank to Mr. Jugaldas Chudasama, M. Pharm. (Plant head), Mr. Vijay Aggarwal, (M.D.) & Mr. Prabhu Narayan Yadav, (Q.A. Exeecutive), Medicef Pharma, Baddi (H.P.), for providing me research facilities to carry out my work and whose inspiring support, valuable suggestions and guidance made me to complete this project successfully.

I express my deep sense of gratitude and thank my guide, Mr. Pratap Singh Rathore, Lecturer, Department of Pharmaceutics, Arya College of Pharmacy, Delhi Road, Kukas, Jaipur (Raj.) 302028

Table 1: Sifting process of API & excipients

S.No.	NAME OF MATERIAL	SIEVE NO.
1.	Amoxycillin Trihydrate	18
2.	Potassium Clavulanate	30
3.	Micro crystalline Cellulose	30
4.	Cross Povidone	30
5.	Colloidal Anhydrous Silica	30
6.	Talcum	60
7.	Colloidal Hydrated Silica	30
8.	Magnesium Stearate	30

Table 2: Pre-compression Studies

S.No.	Tests	F1	F2	F3	F4	F5	F6	F7	F8
1	Bulk Density(gm/ml)	0.45	0.44	0.44	0.46	0.43	0.44	0.45	0.43
2	Tapped Density(gm/ml)	0.52	0.50	0.49	0.51	0.48	0.48	0.49	0.47
3	Carr's Index	13.46	12	10.20	9.80	10.42	8.33	8.16	8.51
4	Hausner's Ratio	1.16	1.14	1.11	1.10	1.11	1.09	1.08	1.09
5	Angle of Repose(degrees)	24	22	21	21	20	21	21	20

Table 3: Composition of all formulations

S. No	Name of Raw Material	F1	F2	F3	F4	F5	F6	F7	F8
1.	*Amoxicillin Trihydrate	575	575	575	575	575	575	575	575
2.	Cross Povidone	20.0 ↑	30.0 ↑	40.0 ↑	50.0 ↑	60.0 ↑	70.0 ↑	80.0 ↑	90.0 ↑
3.	Aerosil (CV17)	15.00	15.00	15.00	15.00	15.00	15.00	15.00	15.00
4.	Magnesium Stearate (CV15)	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00
5.	Talcum (CV12)	0.500	0.500	0.500	0.500	0.500	0.500	0.500	0.500
6.	Sunset Yellow Supra	0.038	0.0386	0.038	0.0386	0.0386	0.0386	0.0386	0.0386
Theoretical weight of 1st layer of tablet		613.54	623.54	633.54	643.54	653.54	663.54	673.54	683.54
1.	*Potassium Clavulanate	304	304	304	304	304	304	304	304
2.	Talcum (CV12)	0.500	0.500	0.500	0.500	0.500	0.500	0.500	0.500
3.	MCC	90.00 ↓	80.00 ↓	70.00 ↓	60.00 ↓	50.00 ↓	40.00 ↓	30.00 ↓	20.00 ↓
4.	Aerosil (CV17)	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00
5.	Celmix DS	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00
6.	Magnesium Stearate (CV15)	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00
Theoretical weight of 2nd layer of tablet		417.50	407.50	397.50	387.50	377.50	367.50	357.50	347.50
Total weight of tablet		1031.04	1031.04	1031.04	1031.04	1031.04	1031.04	1031.04	1031.04

Table 4: Shows Post compression studies of formulation F1-F8 & MP (Marketed Preparation)

TEST		F1	F2	F3	F4	F5	F6	F7	F8	MP
Avg.Wt (mg)		1031	1030	1032	1031	1032	1030	1031	1031	1030
Hardness(Kg/cm^3)		8	8	8	8	8	8	8	8	8
Friability(%)		0.14	0.15	0.18	0.14	0.19	0.12	0.16	0.16	0.19
Length(mm)		19.29	19.31	19.30	19.30	19.29	19.30	19.30	19.31	19.31
Thickness(mm)		6.7	6.7	6.8	6.7	6.8	6.7	6.8	6.7	6.8
Width(mm)		9.0	9.1	9.0	9.1	9.1	9.1	9.0	9.1	9.2
Disintegration		07.54	07.57	07.54	07.56	07.52	07.50	07.23	06.56	08.50
ERH(%)		0.06	0.07	0.06	0.06	0.05	0.07	0.07	0.08	0.09
Assay	Amoxycillin	97.22	97.38	98.52	98.68	98.83	99.20	99.58	99.88	98.51
	Pot. Clav.	95.15	95.46	96.08	96.39	98.03	98.34	98.55	99.43	98.92

Table 5: Shows % Dissolution of F1-F8

Formulation		10 min.	20 min.	30 min
F1	Amoxycillin	81.537	82.921	83.858
	Pot. Clavulanate	81.746	82.087	83.104
F2	Amoxycillin	82.435	83.498	86.046
	Pot. Clavulanate	82.526	83.756	85.970
F3	Amoxycillin	83.347	85.172	87.213
	Pot. Clavulanate	83.294	86.718	87.403
F4	Amoxycillin	84.180	85.782	88.962
	Pot. Clavulanate	87.568	88.542	89.409
F5	Amoxycillin	89.025	90.951	93.077
	Pot. Clavulanate	90.890	91.527	94.282
F6	Amoxycillin	90.654	93.457	95.743
	Pot. Clavulanate	92.345	94.258	95.980
F7	Amoxycillin	93.521	95.243	96.174
	Pot. Clavulanate	95.128	96.795	97.299
F8	**Amoxycillin**	**95.251**	**97.125**	**99.093**
	Pot. Clavulanate	**97.024**	**98.104**	**99.183**

Table 6: Shows Accelerated Stability Data for Bilayered Tablets

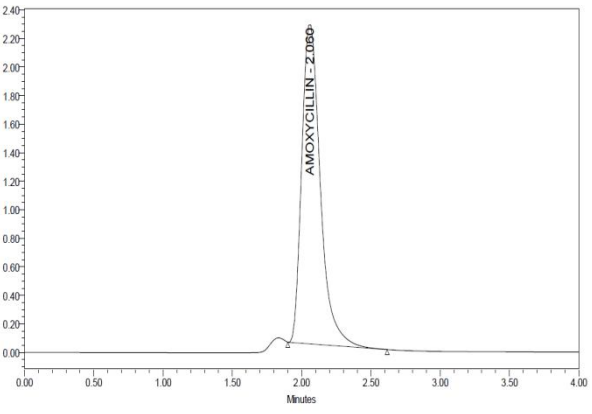
Product name	:	**Amoxycillin & Potassium Clavulanate Bilayered Tablets IP 625 mg**			
Batch No.	:	**BF8**			
Label claim	:	**Each Bilayered Tablet Contains:** Amoxycillin Trihydrate IP eq to. Amoxycillin 500 mg Potassium Clavulanate Diluted IP eq to Clavulanic Acid 125 mg	**Storage Condition**	:	**Temp. 40° ± 2°C and**

Parameter	Specification	Initial	01 Month	02 Months	03 Months	06 Months
Description	One layer white coloured, and other layer sunset yellow coloured, elongated, biconvex, Free from any obvious defects.	Complies	Complies	Complies	Complies	Complies
Identification	To meet the test.	Complies	Complies	Complies	Complies	Complies
Average Weight	1030 mg ± 2%	1031.10mg	1031.30mg	1030.9mg	1031.6mg	1030.7mg
Disintegration Time	NMT 30.0 minutes.	6.54minutes	6.53minutes	6.52minutes	6.54minutes	6.55minutes
Dissolution	NLT 90.0% of claim in 30 minutes.	Clav: Min-98.49%, Max-99.34% Amoxy: Min-98.31%, Max-99.27%	Clav:98.92% Amoxy:98.89 %	Clav:98.61% Amoxy:98.51 %	Clav:98.29% Amoxy:98.23%	Clav:97.81% Amoxy-97.72%
Water	Not more than 10 % w/w	7.56%w/w	7.26%w/w	7.60%w/w	7.69%w/w	7.76%
Microbiological Quality Total Bacterial Count Total Fungal Count *E. coli*	Not more than 1000 cfu/g Not More than 100 cfu/g Should be absent.	141cfu/g Nil Absent	135cfu/g Nil Absent	138cfu/g Nil Absent	132cfu/g Nil Absent	130cfu/g Nil Absent
Assay **Each Bilayered tablet Contains** Amoxycillin Trihydrate IP eq to. Amoxycillin 500 mg Potassium Clavulanate Diluted IP eq to Clavulanic Acid 125 mg	 90% to 120% 90% to 120%	 99.61% 99.57%	 99.02% 99.11%	 98.79% 98.67%	 98.23% 98.17%	 97.56% 97.43%
REMARK: The product is stable as per above stability data.						

Table 7: Shows Accelerated Stability Data for Marketed Preparation

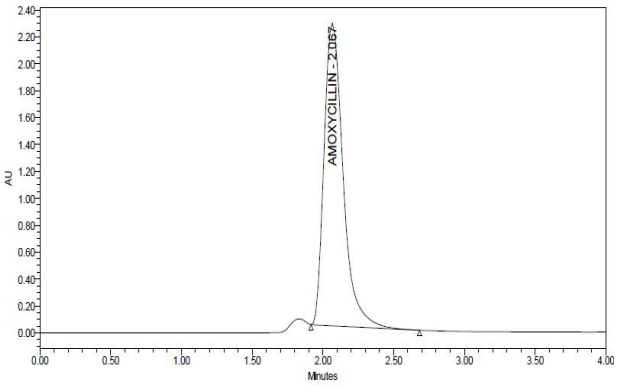
Product name	:	**Amoxycillin & Potassium Clavulanate Tablets IP 625 mg**			
Batch No.	:	**Marketed Preparation**			
Label claim	:	**Each Tablet Contains:** Amoxycillin Trihydrate IP eq to. Amoxycillin 500 mg Potassium Clavulanate Diluted IP eq to Clavulanic Acid 125 mg	**Storage Condition**	:	**Temp. 40° ± 2°C**

Parameter	Specification	Initial	01 Month	02 Months	03 Months	06 Months
Description	White coloured, elongated, biconvex, Free from any obvious defects.	Complies	Complies	Complies	Complies	Complies
Identification	To meet the test.	Complies	Complies	Complies	Complies	Complies
Average Weight	1030 mg ± 2%	1032.40mg	1031.28mg	1031.90mg	1031.60mg	1031.55mg
Disintegration Time	NMT 30.0 minutes.	8.50minutes	8.38minutes	8.47minutes	8.49minutes	8.57minutes
Dissolution	NLT 90.0% of claim in 30 minutes.	Clav: Min-98.21%, Max-99.41% Amoxy: Min-98.02.%, Max-99.19%	Clav:98.53% Amoxy:98.47 %	Clav:98.12% Amoxy:98.08 %	Clav:97.74% Amoxy:97.56 %	Clav:97.06% Amoxy-96.98%
Water	Not more than 10 % w/w	7.71%w/w	7.59%w/w	7.47%w/w	7.85%w/w	7.96%
Microbiological Quality Total Bacterial Count Total Fungal Count *E. coli*	Not more than 1000 cfu/g Not More than 100 cfu/g Should be absent.	141cfu/g Nil Absent	134cfu/gm Nil Absent	132cfu/gm Nil Absent	139cfu/gm Nil Absent	136cfu/g Nil Absent
Assay **Each Tablet Contains** Amoxycillin Trihydrate IP eq to. Amoxycillin 500 mg	90% to 120%	98.51%	98.67%	98.13%	97.53%	96.65%
Potassium Clavulanate Diluted IP eq to Clavulanic Acid 125 mg	90% to 120%	98.92%	98.61%	98.07%	97.42%	96.49%
REMARK: The product is stable as per above stability data.						



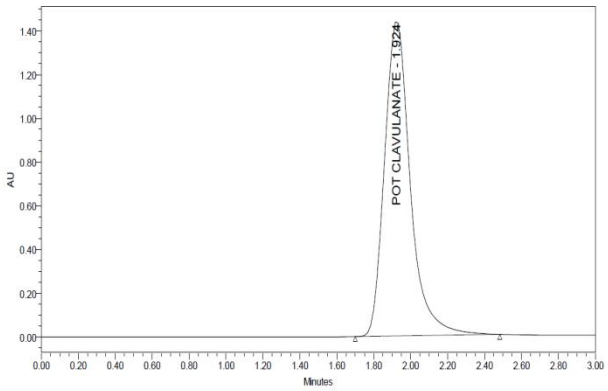
	Peak Name	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	AMOXYCILLIN	2.060	20801626	100.00	2247875	100.00

Fig1: Standard curve of Amoxycillin trihydrate



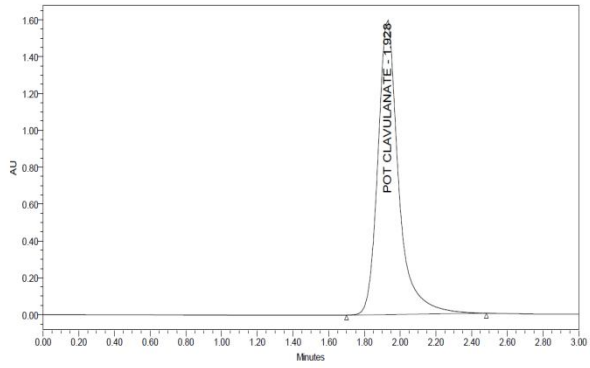
	Peak Name	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	AMOXYCILLIN	2.067	21071004	100.00	2251764	100.00

Fig 2: Curve of sample of Amoxycillin



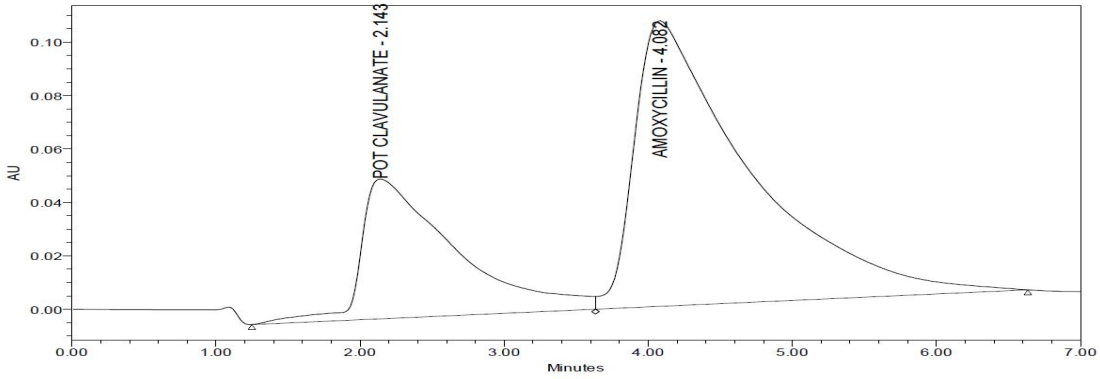
	Peak Name	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	POT CLAVULANATE	1.924	13967685	100.00	1443751	100.00

Fig 3: Standard Curve of Potassium Clavulanate



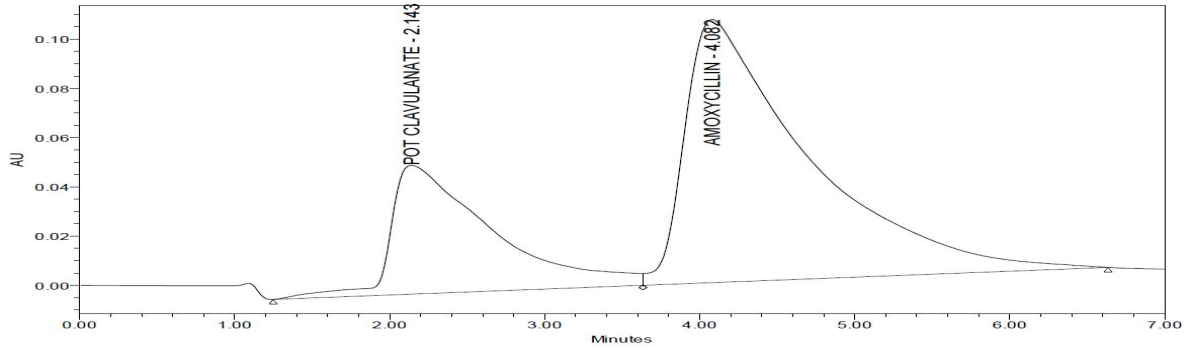
	Peak Name	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	POT CLAVULANATE	1.928	12864556	100.00	1599933	100.00

Fig 4: Curve of Sample of Potassium Clavulanate



	Peak Name	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	POT CLAVULANATE	2.143	2365007	28.59	52404	32.89
2	AMOXYCILLIN	4.082	5905915	71.41	106933	67.11

Fig. 5: Standard Curve of Mixture of Amoxycillin & Potassium Clavulanate



	Peak Name	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	POT CLAVULANATE	2.143	2365007	28.59	52404	32.89
2	AMOXYCILLIN	4.082	5905915	71.41	106933	67.11

Fig. 6: Curve of Mixture of Amoxycillin & Potassium Clavulanate

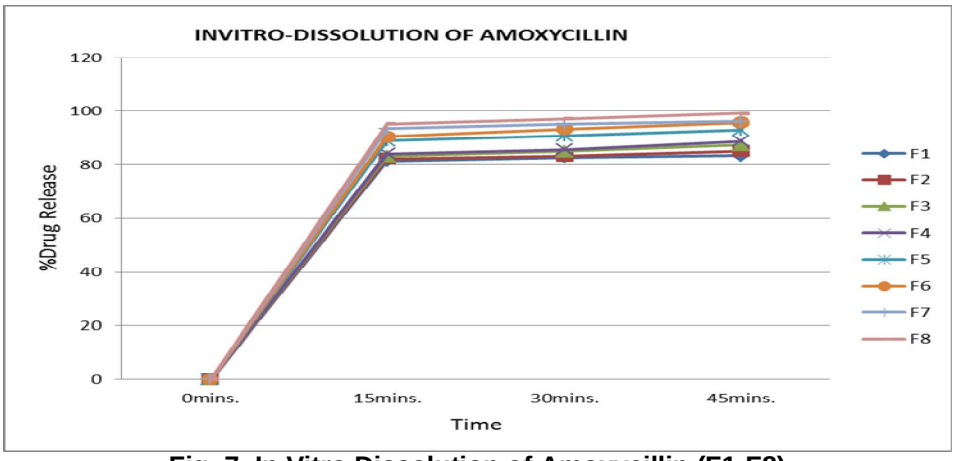


Fig. 7: In Vitro Dissolution of Amoxycillin (F1-F8)

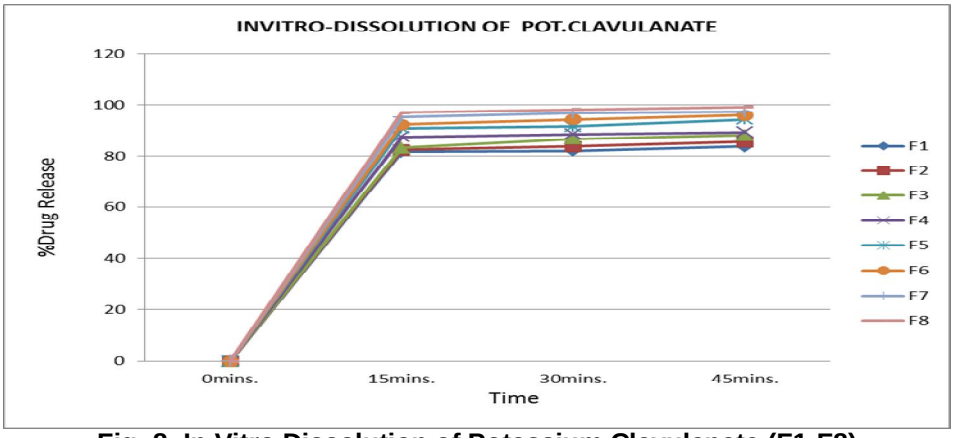


Fig. 8: In Vitro Dissolution of Potassium Clavulanate (F1-F8)

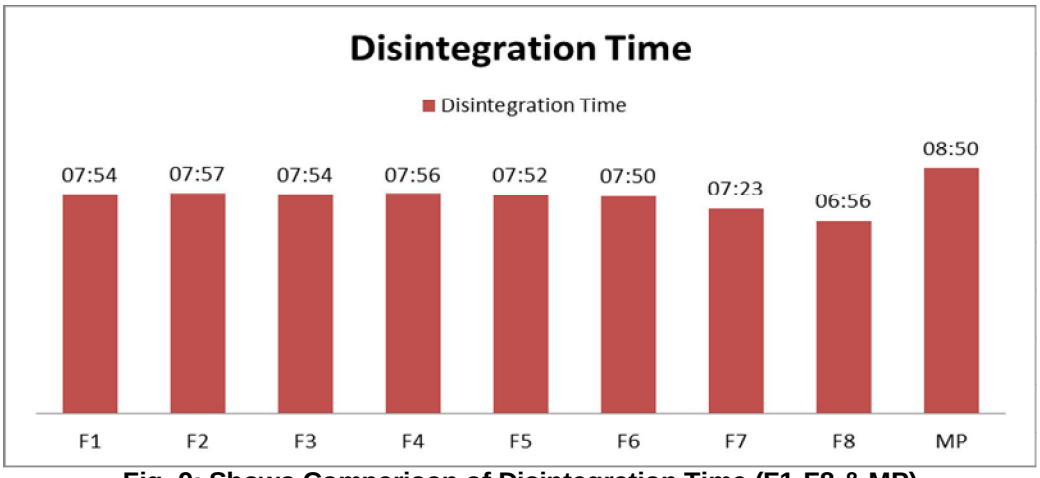


Fig. 9: Shows Comparison of Disintegration Time (F1-F8 & MP)

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