Research Article

Formulation and In Vitro Bioequivalence Study of Amoxycillin and Potassium Clavulanate Chewable Tablet

Mohit kumar[1]*, Jugaldas Chudasama[2], Ajay Bilandi[1], Vijay aggarwal[2], Prabhu Naryan[2] and Mahesh Kataria[1]

[1]Seth G.L. Bihani S.D. College of Technical Education, Institute of Pharmaceutical Science & Drug Research, Sriganganagar, Himachal Pradesh, India.
[2]Medicef Pharma, Jharmajri, Baddi, Himachal Pradesh, India.

ABSTRACT
The objective of present study was to develop the formulation of chewable tablet of Amoxycillin & Potassium clavulanate and perform the in vitro bioequivalence study with trying to enhance the bioavailability of innovator formulation. Reduction in the dose of Amoxycillin and potassium clavulanate tablet was possible by developing chewable tablet. Chewable tablets are the tablets which are need to be broken and chewed in between the teeth before ingestion. These tablets are given to the adults who dislike swallowing and to the children who have difficulty in swallowing and Total 10 formulations were made with different concentration of Micro crystalline cellulose & Croscarmellose sodium by dry granulation method. The formulations were evaluated for weight variation, hardness, friability, disintegrating time, dissolution study. All the formulations shows uniform weight, hardness and friability data indicates good mechanical resistance of the tablet. All the tablets were disintegrated between 3-5 min. The optimized (F10) formulation showed good disintegration time and release profile with maximum drug being released than marketed preparation at all time intervals.

Keywords: Amoxicillin Trihydrate, Potassium Clavulanate, Microcrystalline Cellulose.

1. INTRODUCTION

In the world of pharmacy around 80% of the tablets manufactured are ingested orally. Administration of drugs through oral route is the most common and the easiest way to administer a drug. However, geriatric and bedridden pediatric, patient shows inconvenience swallowing conventional tablets or due to difficulties in swallowing with lesser amounts of water with the medication, because of large tablet size difficulties in swallowing, unable to tolerate the taste of many drugs when formulated as liquid dosage forms, resulting in poor patient compliance. The rationalized approach in case of medication leads to the development of chewable tablets. These are manufactured so that they may be chewed in the mouth producing a pleasant tasting residue in the oral cavity that is easily swallowed and does not leave a bitter a unpleasant taste. Chewable tablets are the tablets which are need to be broken and chewed in between the teeth before ingestion. These tablets are given to the adults who dislike swallowing and to the children who have difficulty in swallowing and. For Successfully tablet formulation development involves the careful selection of ingredients in order to manufacture a robust solid dosage form. Choosing the appropriate excipients to perform a specific function in a tablet formulation, such as disintegration or lubrication can be critical to achieving acceptable manufacturing performance. Sweeteners, both naturally occurring and synthetic, are one type of functional excipients commonly used in chewable tablet formulations to mask unpleasant tastes and facilitate pediatric dosing. Ideally chewable formulations should have smooth texture upon disintegration, pleasant taste and no bitter and unpleasant after taste. Upon chewing, they are broken down in the mouth and release their ingredients in the process and therefore, do not have much lag time as required for the disintegration of tablets before absorption from stomach.

In combination of Amoxycillin & Potassium clavulanate is available in various dosage forms like film coated tablet, dry syrup, suspension. Due to high dose 625mg bis in die (for adults), tablet having a long and wide in size of 1 to 1.5 gm, so it is difficult to some patients (geriatric, bedridden, pediatric) to swallow the tablet. So in this research work prepared a chewable tablet of Amoxycillin & Potassium Clavulanate tablet. The antibiotics are available in various dosage forms.

Amoxycillin is an antibiotic of the penicillin type. It is effective against different bacteria such as H. influenzae, N. gonorrhea, E. coli Pneumococci, Streptococci, and certain strains of Staphylococci, It is used in the treatment of patients with acquired pneumonia or acute bacterial sinusitis due to confirmed or suspected beta lactamase pathogens. Bacterial resistance to the beta-lactam group of antibiotics is frequently due to the production of beta-lactamase which brings about inactivation of the anti-biotic. Potassium Clavulanate is a naturally occurring inhibitor of beta lactamase which is capable of rendering penicillin and cephalosporin resistant organisms sensitive. Prevent bacterial regrowth when free drug levels fall below the minimum inhibitory concentration (MIC).

In-vitro Bioequivalence

According to US FDA two formulations are said to be bioequivalent if "The rate and extent of absorption of the test drug do not show a significant difference from the rate and extent of absorption of the reference drug, when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either single dose or multiple dose. For two orally administered drug products to be bioequivalent, they should be pharmaceutical alternative or pharmaceutical equivalent must exhibit the rate and extent of absorption.

2. PREFORMULATION STUDY

2.1 Identification of Amoxycillin & Potassium Clavulanate By HPLC

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

(a) Methodology & Procedure

In identification of APIs the column was C18 type, mobile phase was 7.8 gm disodium hydrogen Ortho Phosphate, 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.

Mobile phase was prepared with 7.8 gm disodium hydrogen ortho phosphate. HPLC column was firstly wash with hot water and then with mobile phase for remove the previous solvents, and then saturated the column to obtained the base line after that taken one trail to check retention time then run the standard and test product.

2.2Evaluation of Granules

Bulk density was determined with 20 gm sample. Take 20 gm sample, after weighing sample was measured in measuring cylinder in ml and calculate the bulk density. After that Tap measuring cylinder for 100 times then note the volume of powder after tapping, by this determine the Tapped density. By the readings of bulk and tapped density determined the Carr's and Hausner's ratio.

(b) Bulk density

The bulk density of a powder is the ratio of the mass of an untapped powder sample and its volume including the contribution of the interparticulate void volume. The bulk density is expressed in grams per milliliter (g/ml).

(c) Tapped Density

The tapped density is an increased bulk density attained after mechanically tapping a container containing the powder sample. The tapped density is obtained by mechanically tapping a graduated measuring cylinder or vessel containing the powder sample. After observing the initial powder volume or mass, the measuring cylinder or vessel is mechanically tapped, and volume or mass readings are taken until little further volume or mass change is observed.

(d) Carr's Index

The interparticulate interactions influencing the bulking properties of a powder are the interactions that interfere with powder flow, a comparison of the bulk and tapped densities can give a measure of the relative importance of these interactions in a given powder.. Carr's index limit-5-11(Excellent), 12-16(Good), 18-21 (Fair to passable).

$$\text{CARR'S INDEX (\%)} = \frac{\text{(TAPPED DENSITY – POURED DENSITY)}}{\text{TAPPED DENSITY}} \times 100$$

(e) Hausner's Ratio

It is Tapped density/ bulk density. It is depend upon these two densities. Hausner's Ratio limit: 1.00-1.11(Excellent), 1.12-1.18(Good), 1.19-1.25(Fair)

(f) Angle of Repose

Angle of repose was determined by funnel method.By determining Angle of Repose determine the flow properties of powder.

Greater angle of repose indicate poor flow. It should be less than 30°. & can be determined by following equation.
tan θ = h/r., where, θ = angle of repose,
h=height of pile, r= radius.
Limit- <25 (Excellent)25-30 (Good),
30-40 (passable) (16).

3. MATERIALS AND METHODS

3.1 MATERIALS

Amoxycillin Trihydrate & Potassium Clavulanate was produced from DSM Sinochem Pharma, Microcrystalline cellulose from Mingtai chem. Cells co. Ltd., Croscarmellose sodium from Base Chemicals, Magnesium stearate from Suzong Chemicals, Aspartame from Biocon Ltd and Aerosil from Wacker.

3.2 Method Dry Granulation

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

Procedure

Sifting is the first step of formulation of Amoxycillin and clavulanate chewable tablet was sifting (Table 1) Then Dry Blending, In this step Load the sifted material of step first in the Octagonal blender & mix for 15 minutes. Then Compaction by roll compactor at the temperature of 23-25C. Then Granulation, Pass the compacted material through Oscillatory Granulator through 2.5 mm screen. Then Sifting, Sift the milled material of previous step through 18 # S.S. mesh. Then Drying, After sifting Dry the granular power in Vacuum Tray Dryer for Two hours at 60^0C temperature and vacuum at 710 ± 10 mm Hg. Then Sifting, Sift Potassium Clavulanate through sifter fitted with sieve # 30.Then Blending, After Sifting Load the Drying material in the Octagonal blender and add Potassium Clavulanate, Aerosil & Magnesium Stearate mix for 30 minutes. After that Compression, final step was compression of tablet of 27 stations D tooling machine is used to formulate Amoxycillin & potassium clavulanate chewable tablet.

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.	Croscarmellose sodium	30
5.	Aerosil	30
6.	Talcum	60
7.	Magnesium Stearate	30

Table 2: Composition of all formulations of 625mg Chewable tablet

S.No.	Name of Raw Material	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)	F10 (mg)
01.	Amoxycillin trihydrate	575	575	575	575	575	575	575	575	575	575
02.	Potassium Clavulanate	304	304	304	304	304	304	304	304	304	304
03.	MCC	27.32	27.32	27.32	27.32	27.32	26.32	25.32	24.32	23.32	22.32
04.	Croscarmellose sodium	51	52	53	54	55	55	55	55	55	55
05.	Talcum	1	1	1	1	1	1	1	1	1	1
06.	Aerosil	25	23	22	21	20	27	28	29	30	31
07.	Magnesium Stearate	6.60	6.60	6.60	6.60	6.60	6.60	6.60	6.60	6.60	6.60
08.	Aspartame	27	27	27	27	27	27	27	27	27	27
09.	Strawberry	14	14	14	14	14	14	14	14	14	14

4. Evaluation of tablet

4.1 Disintegration time

It was determined by using USP disintegrator by using 6 tablets at the temperature of 37 C. The Batch F10 shows best disintegration time (3.41 min.) and marketed formulation disintegrated at 8.50 min. (Figure 9).

4.2 Average weight

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance (Table no. 4).

4.3 Friability

This was determined by weighing 10 tablets after dusting, placing them in the friabilator and ro-tating the plastic cylinder vertically at 25 rpm for 4 min. After dusting, the total remaining weight of the tablets was recorded and the percent friability was calculated, the friability was ranged from 0.18 to 0.21(Table 4).

4.4 Hardness

The resistance of tablets to shipping or breakage, under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of tablet of each formulation was measured by Monsanto hardness tester10. The hardness was measured in terms of kg/cm2, it was recorded in between 4 to 7(Table No. 4).

4.5 Thickness,Width,Length

These were determined using Vernier caliper. Five tablets were randomly selected for the determination of thickness and diameter with the help of vernier caliper(Table No. 4).

4.6 In-vitro release study

The release of Amoxycillin & Potassium Clavulanate from Chewable 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 determine % Release at HPLC.

RESULT

Preformulation study

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

Solubility

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

Identification

Identified successfully. 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

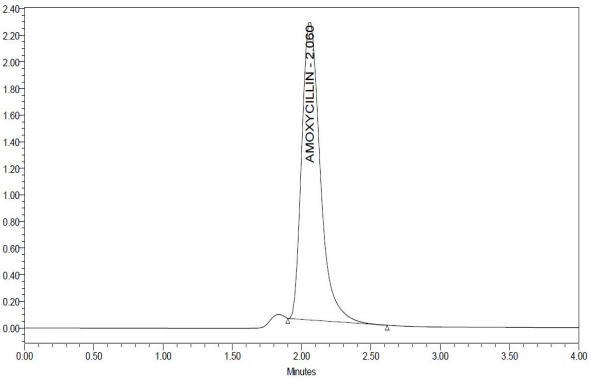
Evaluation of granules were determined successfully. The Results were in limits, The Carr's index of all batches was 9 to 13 it was in the limit and the Hausner's ratio was also in limit, it was 1.10-1.25.Angle of repose was also successfully determined, it was 22-22.6(Table 3).

Evaluation of tablets

Tablets were evaluated for weight variation, hardness, friability, Disintegration time, Equivalent Relative Humidity, Assay and dissolution study. Tablets were having uniform weight, hardness and friability data indicates 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. Length of all batches were found from 19.2 to 19.3, Thickness was from 6.7 to 6.9, width of all batches including marketed formulation were 9.1 to 9.2. Disintegration time was found in between the 3.41 to 4.56 mi. The Batch F10 shows best disintegration time it was 3.41 min and disintegration of marketed formulation was 8.50 min which was greater than F10 batch. The tablets also evaluated for the %ERH, it was with in the limit(0.05 to 0.07) and uniformity of weight and found to be within the limit.(Table No. 4)

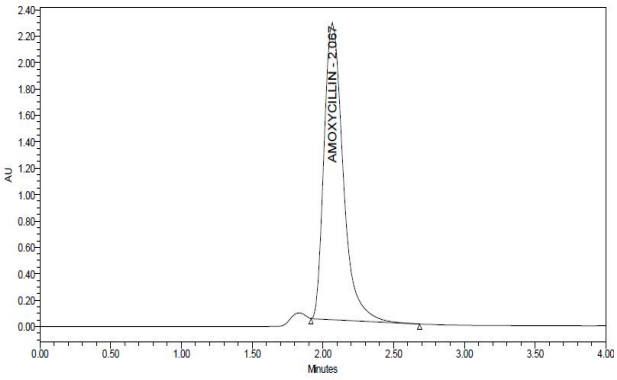
The % release of batch F1-F4 were 70-82% and from batch F6-F10 was within the limit of 90-100%.Batch F10 shows better release compare to marketed formulation. Batch F10 shows 99.68% Amoxycillin (Figure7) & 99.12% of Potassium Clavulanate (Table No.5, Figure 8), Marketed formulation shows 95.593% Amoxycillin & 96.827% of Potassium Clavulanate (Table No.6, Figure 10, 11).

Table No. 6 shows the Comparative Dissolution Profile of Maketed formulation and innovator formulation. At each interval time Innovator formulation shows better release properties than marketed formulation.



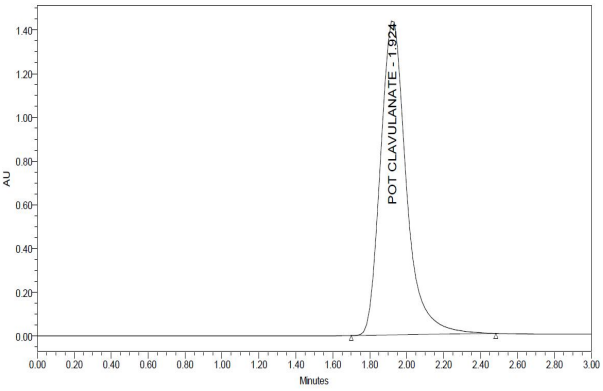
	Peak Name	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	AMOXYCILLIN	2.060	20801626	100.00	2247875	100.00

Fig. 1: Standard curve of Amoxycillin trihydrate



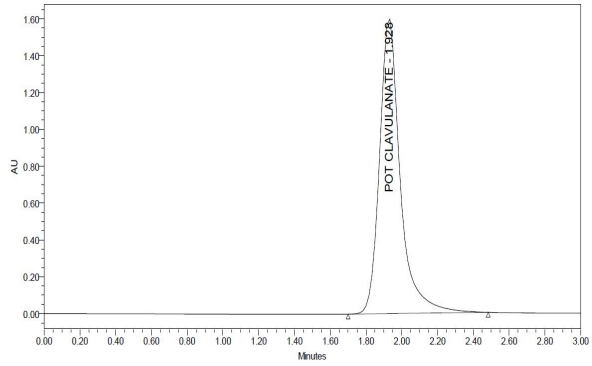
	Peak Name	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	AMOXYCILLIN	2.067	21071004	100.00	2251764	100.00

Fig. 2: Curve of sample of Amoxycillin



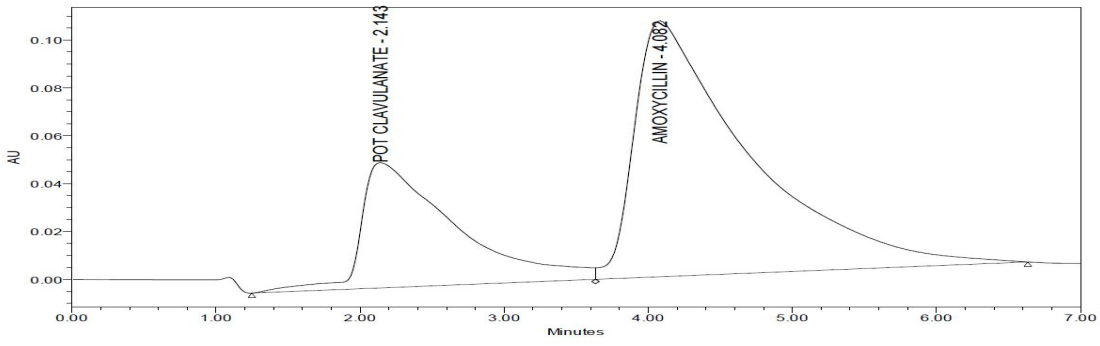
	Peak Name	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	POT CLAVULANATE	1.924	13967685	100.00	1443751	100.00

Fig. 3: Standard Curve of Potassium Clavulanate



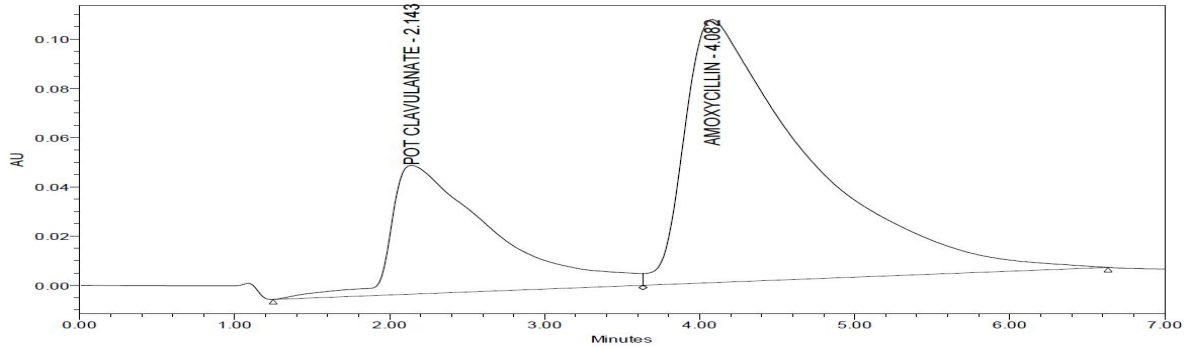
	Peak Name	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	POT CLAVULANATE	1.928	12864556	100.00	1599933	100.00

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

Table 3: Pre compression Studies

S.No.	Test	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	Bulk density(gm/ml)	0.460	0.471	0.460	0.471	0.465	0.462	0.460	0.450	0.465	0.460
2	Tapped density(gm/ml)	0.532	0.522	0.532	0.522	0.536	0.538	0.532	0.535	0.535	0.532
3	Carr's index	13.53	9.77	13.53	9.77	13.24	13.26	13.53	15.88	20.75	13.08
4	Hausner's ratio	1.15	1.10	1.15	1.10	1.25	1.16	1.15	1.17	1.16	1.15
5	Angle of repose(degrees)	22.4	22.5	22	22.2	22.4	22.6	22.4	22.6	22.5	22.4

Table 4: Post compression Studies of formulation F1-F10 & MP

Name of Test		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	MP
Avg.Wt. (mg)		1031	1032	1029	1031	1030	1032	1031	1030	1031	1032	1030
Hardness(Kg/cm^2)		4	4	6	7	5	5	4	5	5	6	7
Friability (%)		0.21	0.18	0.19	0.15	0.15	0.18	0.19	0.19	0.20	0.19	0.19
Length(mm)		19.2	19.3	19.2	19.3	19.3	19.2	19.3	19.3	19.2	19.2	19.3
ERH %		0.05	0.04	0.06	0.05	0.05	0.07	0.08	0.05	0.06	0.05	0.07
Thickness(mm)		6.8	6.9	6.7	6.8	6.7	6.9	6.8	6.7	6.8	6.9	6.8
Width(mm)		9.1	9.1	9.1	9.2	9.1	9.2	9.1	9.1	9.1	9.2	9.2
Disintegration time(Min.)		4.56	4.53	4.54	4.52	4.56	4.50	3.58	3.52	3.48	3.41	8.50
ERH(%)		0.07	0.07	0.08	0.05	0.06	0.07	0.06	0.07	0.08	0.08	0.09
Ass	Amoxycillin (%)	95.1	98.3	98.5	98.7	98.8	98.9	99.1	99.3	99.4	99.5	98.5
	Potassium	97.0	98.2	98.7	98.8	98.9	98.97	99.2	99.36	99.5	99.7	97.1

Table 5: In- Vitro Dissolution Study

FORMULATIONS		AFTER 10MIN. (%)	AFTER 20MIN. (%)	AFTER 30MIN. (%)	AFTER 45MIN. (%)
F1	Amoxycillin	50.458	61.247	65.182	70.764
	Pot. Clav.	52.654	63.429	74.678	75.696
F2	Amoxycillin	55.498	68.525	74.951	75.502
	Pot. Clav.	56.568	69.990	77.527	78.158
F3	Amoxycillin	60.984	68.654	75.902	78.346
	Pot. Clav.	58.732	68.845	78.094	79.228
F4	Amoxycillin	65.954	67.521	75.523	80.417
	Pot. Clav.	68.658	75.828	77.795	82.711
F5	Amoxycillin	72.147	88.921	89.125	90.027
	Pot. Clav.	72.653	90.324	92.104	93.082
F6	Amoxycillin	72.891	89.180	91.782	94.697
	Pot. Clav.	73.672	92.568	93.542	95.263
F7	Amoxycillin	78.658	92.025	93.951	95.843
	Pot. Clav.	78.165	93.890	95.527	96.673
F8	Amoxycillin	78.547	94.654	96.457	97.674
	Pot. Clav.	79.578	95.345	96.258	97.789
F9	Amoxycillin	79.568	95.521	97.243	98.437
	Pot. Clav.	79.175	96.128	97.795	98.499
F10	Amoxycillin	80.732	97.251	98.125	99.685
	Pot. Clav.	85.149	98.024	98.324	99.127

Note: Pot. Clav.= Potassium Clavulanate

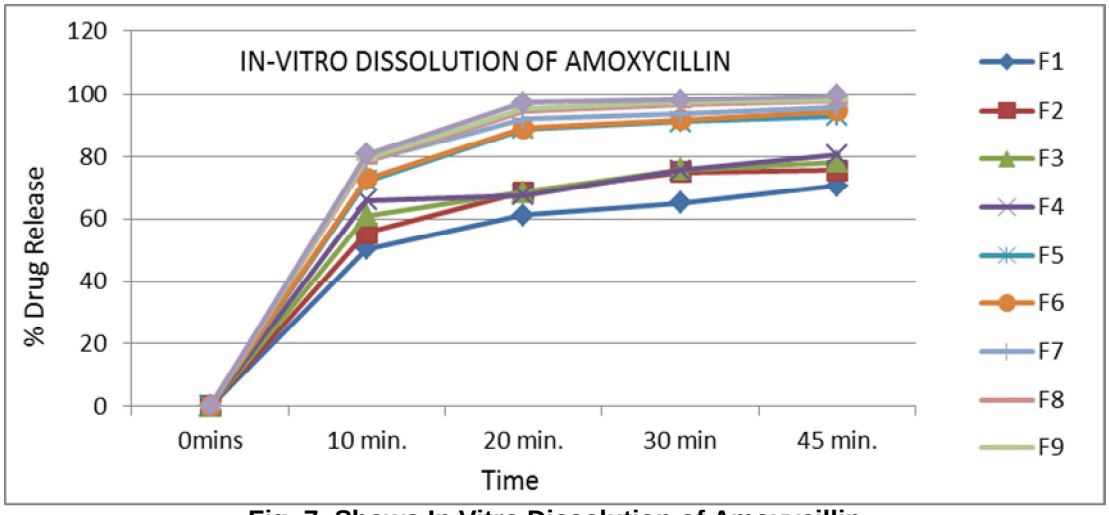


Fig. 7: Shows In Vitro Dissolution of Amoxycillin

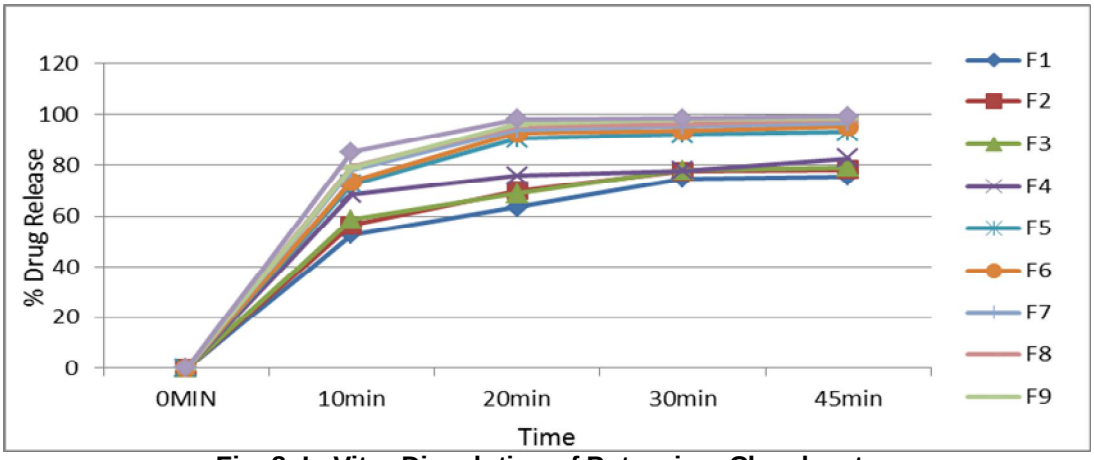


Fig. 8: In Vitro Dissolution of Potassium Clavulanate

Table 6: In-vitro Bioequivalence study

FORMULATION		DISSOLUTION				ASSAY (%)
		10Min.	20Min.	30Min.	45Min.	
INNOVATOR FORMULATION (F10)	Amoxycillin	80.732	97.251	98.125	99.685	99.59
	Potassium Clavulanate	85.149	98.024	98.324	99.127	85.149
MARKETED FORMULATION	Amoxycillin	75.156	90.647	92.913	95.593	98.994
	Potassium Clavulanate	78.274	93.839	95.387	96.807	98.457

NOTE MF = Maketed formulation

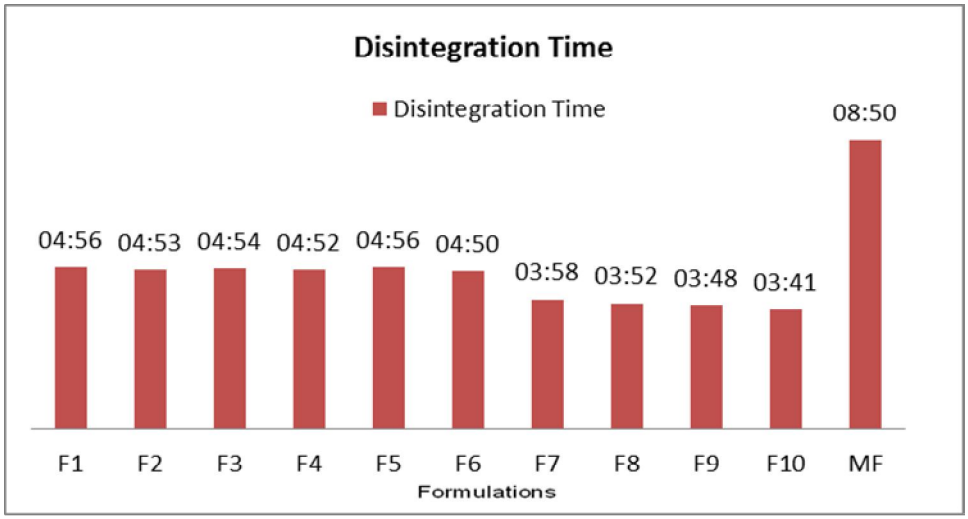


Fig. 9: Shows Comparison of Disintegration Time of F1-F10 & Maketed formulation

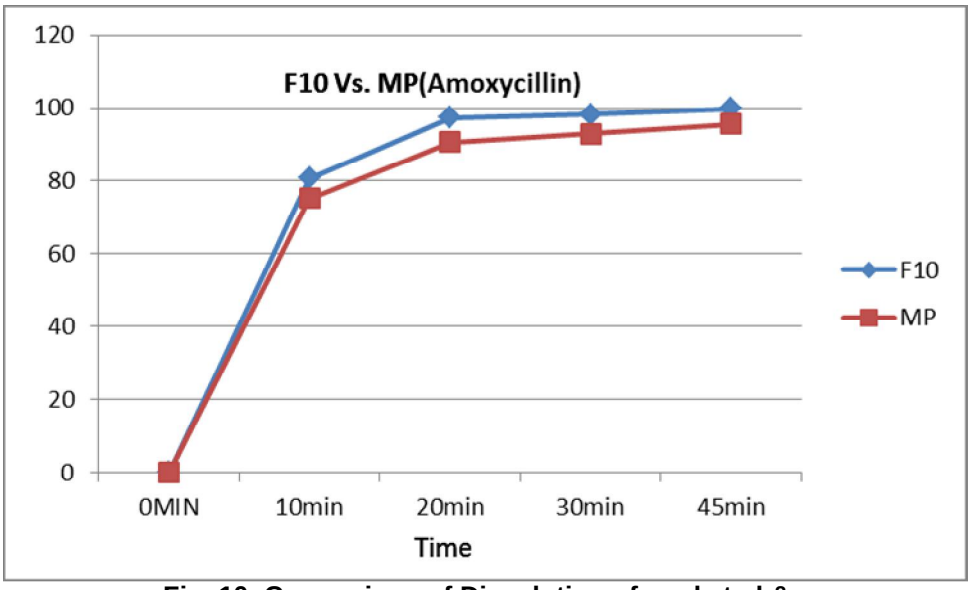


Fig. 10: Comparison of Dissolution of marketed & Innovator product (Amoxycillin)

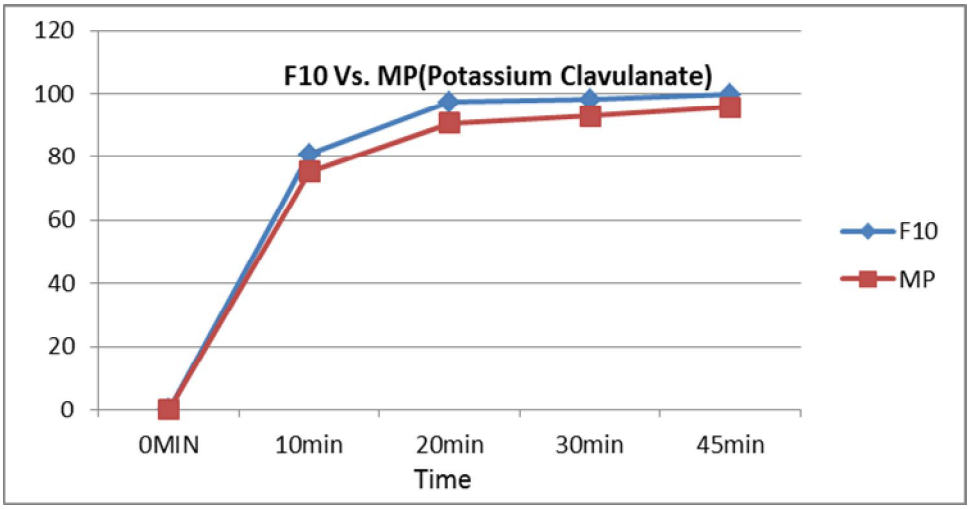


Fig. 11: Comparison of Dissolution of marketed & Innovator product (Potassium Clavulanate)

CONCLUSION

It was concluded that Amoxycillin & Potassium Clavulanate Chewable tablet can be formulated and Reduction in the dose of Amoxycillin and potassium clavulanate tablet possible by developing chewable tablet.

The % release of batch F1-F4 Was Failed and from batch F6-F10 was with in the limit of 90-100%.Batch F10 shows better release compare to marketed formulation. Batch F10 shows 99.68% Amoxycillin & 99.12% of Potassium Clavulanate, marketed formulation shows 98.99% Amoxycillin & 98.55% of Potassium Clavulanate.

ACKNOWLEDGEMENT

I express my heartfelt thank to Mr. Jugaldas Chudasama, M.Pharm, (Plant head), Mr. Vijay Aggarwal, (M.D.) & Mr. Prabhu Narayn 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.Ajay Bilandi, Lecturer, Department of Pharmaceutics, Seth G. L. Bihani S. D. College of Technical Education, Institute of Pharmaceutical Sciences & Drug Research Sriganganagar - 335001 (Raj.).

REFRENCES

1. Adeyeye MC and Britaain HG. Preformulation In Solid Dosage Form Development. Infoma Healthcare.2008;104-107.
2. Aulton ME. Pharmaaceutics: The Science of the Dosage Form Design. Churchill Livingstone, 2003;407-413.
3. British Pharmacopoeia.The Stationery Office on behalf of the Medicines and Healthcare products,2009;1-4.
4. Gad SC. Pharmaceutical Manufacturing Handbook. Johan Wiley & Sons. 2008;253-259.
5. Guideline on The Investigation Of Bioequivalence by European Medicines Agency Pre Authorization Evaluation of Medicines for Human Use.
6. Haidar SH, kwon Hyojong and Lionberger. A text on Bioavailaibility and Bioequivalence. 262-271.
7. Havey AR and Champe PC. Lippincott's illurating Reviews"4th edition, 2009;360-365.
8. Huda N, Jhanker Y and Daula S. Comparative Dissolution Study of different brands of Amoxicillin trihydrate capsules available in Bangladesh. Stamford journal of pharmaceutical sciences.2002;2(2):72-75.
9. Jagdale S, Gattani M and Bhavsar D. Formulation and evaluation of chewable tablet of levamisole.International Journal of Research in Pharmaceutical Sciences. 1(3):282-289.
10. Kalvimoorthi V, Thamizh Mozhi M and Rajasekaran M. Formulation and In-Vitro Evaluation of Amoxicillin Clavulanate Potassium Tablet. International Journal of Analytical, Pharmaceutical and Biomedical Sciences. 2012;1(3):96-100.
11. Kaur SM, Rao R and Nanda S. Amoxicillin A broad Spectrum Antibiotic. International Journal of

Pharmacy and Pharmaceutical Sciences. 2011;3(3):30-35.
12. Odulaja J, Paul A and Akinleye M. Quality Assessment of Amoxicillin-Clavulanate Potassium Tablets in lagos Nigeria. Journal of Chemical and Pharmaceutical Research. 2012;4(12):5032-5038.
13. Prasad SG, Das P and Kiran R. Formulation and Evaluation of Chewable Tablet of Montelukast. International Jounal of Research in Pharmacy and Biotechnology. 2012;1(1):32-37.
14. Rowe RA, Sheskey P and Owen S. Hnadbook of Pharmaceutical Excipients, fifth edition, Pharamaceutical Press. 2006;210-221, 430-432..
15. Swamivelmanickam M, Valliappan K and Reddy PG. Preformulation Studies for Amoxicillin Trihydrate and Dicloxacillin sodium as Mouth Dissolve tablets.International Journal of ChemTech Research. 2009;1(4):1032-1035.
16. The Indian Pharmacopoeia, Ghaziabad: The Indian Pharmacopoeia Commission. 2007;2:99-108.
17. Tukaram A, Hamsa L and Nagesh M. Bioequivalence Testing" Journal of Bioequivalence & Bioavailability. 2010;2(5):98-101.
18. U.S.Pharmacopoeia, Amoxicillin and Clavulanate Potassium. The united states Pharamacopoeial convention. 2007;1-11.