

FORMULATION AND EVALUATION OF FAST DISSOLVING TABLETS OF AMOXYCILLIN TRIHYDRATE AND POTASSIUM CLAVULANATE

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Received: 27 Nov 2016, Revised and Accepted: 23 Jan 2017

ABSTRACT

Objective: The present work is aimed to formulate fast dissolving stable tablet formulation a preferred combination of Amoxicillin trihydrate (Beta-lactum antibiotic) and Potassium clavulanate (Beta-lactum inhibitor) by using various super disintegrants.

Methods: Fast dissolving tablets are prepared by direct compression method using super disintegrants i.e. sodium starch glycolate, crospovidone, croscarmellose sodium. Aspartame as a sweetener and trusil mango flavor were used to increase palatability. Reduction in the dose of Amoxicillin trihydrate and Potassium clavulanate tablet was possible by developing fast dissolving tablet.

Results: The powder blends were subjected to various pre-formulation evaluations such as, tapped density, bulk density, hausner's ratio, the angle of repose and compressibility index. The prepared Amoxicillin trihydrate and Potassium clavulanate fast dissolving tablets were evaluated for thickness, weight variation, friability, disintegration time, hardness, wetting time and *in vitro* drug release. All fast dissolving tablet formulations shown uniform weight, hardness and friability data indicates the good mechanical resistance of the fast dissolving tablet. Fast dissolving tablets were disintegrated between 25-50 second and *in vitro* disintegration time of the best fast disintegrating tablets was found to be 25 second.

Conclusion: Amoxicillin trihydrate and Potassium clavulanate fast dissolving tablets were found to be of good quality fulfilling all the needs for fast dissolving tablets. The optimised (F-4) formulation had shown best disintegration time and released profile with a maximum *in vitro* drug release as compare to marketed preparation at all time intervals of *in vitro* drug release.

Keywords: Fast dissolving tablets, Amoxicillin trihydrate, Potassium clavulanate, Sodium starch glycolate, Crospovidone, Croscarmellose sodium

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DOI: <http://dx.doi.org/10.22159/ijcpr.2017v9i2.17385>

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 paediatric, the 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 the case of medication leads to the development of fast dissolving (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 or unpleasant taste. Fast dissolving tablets are the tablets which are needed 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. 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 or unpleasant aftertaste. 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 the stomach.

The aim of the research work is to formulation and evaluation of Amoxicillin trihydrate and Potassium clavulanate fast dissolving tablet [1, 2].

In a combination of Amoxicillin trihydrate and Potassium clavulanate is available in various dosage forms like film coated tablet, modified release tablet, dry syrup, suspension. Due to high dose 625 mg bis in die (for adults), the 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 fast dispersible tablet of Amoxicillin trihydrate and Potassium clavulanate tablet. The antibiotics are available in various dosage forms. Amoxicillin is an antibiotic of the penicillin type. It is effective against different bacteria such as *H. influenzae*, *N. gonorrhoea*, *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. [1, 2] Amoxicillin-Clavulanic acid dispersible tablet is used to treat certain infections caused by bacteria, including infections of the ears, lungs, sinus, skin, and urinary tract [3]. Bacterial resistance to the beta-lactam group of antibiotics is frequently due to the production of beta-lactamase which brings about inactivation of the antibiotic. 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) [1, 2].

MATERIALS AND METHODS

Materials

Drugs; Amoxicillin trihydrate, Potassium clavulanate and excipients; sodium starch glycolate, crospovidone, cross carmellose sodium, colloidal silicon dioxide, talcum, mannitol, magnesium stearate, microcrystalline cellulose (MCC), aspartame, trusil mango flavour

were a gift from Brook laboratories limited, Baddi, District-Solan (HP).

Pre-formulation studies

Identification and characterization of drugs

Calibration curve of amoxicillin trihydrate and potassium clavulanate [1-12]

Preparation of stock solution

Accurately weighed amount of 100 mg drug was transferred into a 100 ml volumetric flask. Few ml was added to dissolve the drug and volume was made up to 100 ml with 6.8 pH phosphate buffer. The resultant solutions have the concentration of 1 mg/ml which was labelled as 'stock'.

Preparation of working standard solution

From this stock solution, 10 ml was taken and diluted to 100 ml with 6.8 pH buffer which has given the solution having the concentration of 100 mg/ml of both drugs, separately.

Estimation of λ_{max}

The stock solution was used for the estimation of λ_{max} by using UV spectrophotometer with a suitable dilution of both drugs, separately.

Preparation of serial dilutions for standard calibration curve

Necessary dilutions were made by using this second solution to give the different concentration of Amoxicillin trihydrate (2-10 mg/ml) solutions and Potassium clavulanate (2-10 mg/ml) solutions. The resultant solution is scanned for maximum absorption from 200 to 400 nm wavelength range.

Solubility [3-6]

The solubility of the drugs was determined in 5 different media. The different media used were water, 0.1N HCL, pH 4.5 acetate buffer, pH 6.8 phosphate buffer and pH 7.2 phosphate buffer. An excess quantity of drug was taken in 10 ml of different solutions in a shaking water bath (100 agitations per minute) for 24 h at room temperature. The solution was then passed through a whatmann (No. 1) filter and the amount of the drug dissolved was analyzed.

Flow properties evaluation [10-16]

Preformulation studies are the first step in the rational development of dosage form of a drug substance. The objective of preformulation studies are to develop a portfolio of information about the drug substance so that this information useful to develop formulation. Preformulation can be defined as the investigation of physical and chemical properties of drug substance alone and when combined with excipients. Preformulation investigations are designed to identify those physicochemical properties of excipients that may influence the formulation design, method of manufacture, and pharmacokinetic-biopharmaceutical properties of the resulting product. Following are the test performed for the pre-formulation study.

Bulk density [10, 14]

An accurately weighed 10 g quantity each of the powder samples were placed into a clean 50 ml measuring cylinder and the volume, which was previously passed through sieve # 30 [USP]. The volume occupied by each of the samples without tapping was noted. The bulk density was expressed in grams per milliliter (g/ml). The volume measure was called as the bulk volume and the bulk density is calculated by following formula;

$$\text{Bulk density} = \text{Weight of powder/Bulk volume} \text{ -----(1)}$$

Tapped density [10, 12, 14]

A 50 ml measuring cylinder was filled with 10 gm quantity of powder. The cylinder was tapped 500 times on a hard table top and tapped volume, V_{500} were recorded. The experiment was repeated in triplicates.

Hausner ratio [10, 12, 14]

Hausner ratio is an indirect index of ease of powder flow. It is the ratio of tapped density to the bulk density. It was calculated by the following formula;

$$\text{Hausner ratio} = \text{Td/Bd} \text{ -----(2)}$$

Where, Td = tapped density, Bd= bulk density.

The ideal range of Hausner ratio should be 1.2-1.5.

Carr's index or % compressibility index [10, 14]

It indicates powder flow properties. It is the simple test to evaluate the bulk density and tapped density of a powder and the rate at which it packed down. The Carr's compressibility index was calculated by calculating the tapped and bulk density using the 100 ml measuring cylinder. Compressibility is calculated by the formula.

$$\text{Carr's index (\%)} = \frac{(\text{Tapped density} - \text{Poured density})}{\text{Tapped density}} \times 100 \text{ ----- (3)}$$

A carr's index greater than 25 is considered to be an indication of poor flowability, and below 15, of good flowability.

Angle of repose [10, 11, 14]

The angle of repose is a relatively simple technique for estimation of the flow property of powder. Powders with a low angle of repose are free flowing, and those with a high angle of repose are poorly flowing powders. 10 gm of granules were passed through the funnel and the pile was formed. For determination of the angle of repose (θ), the blend was poured through the walls of a funnel, which was fixed at a position such that its lower tip was at the height of exactly 2.0 cm above the hard surface. The blends were poured till the time when upper tip of the pile surface touched the lower tip of the funnel. The angle of repose was calculated using following equation.

$$\text{Tan}\theta = (h/r) \text{ -----(4)}$$

Therefore $\theta = \text{Tan}^{-1} h/r$

Where; θ = Angle of repose, h = height of pile, r = radius of pile.

Drug-polymer interaction by fourier-transform infrared (FTIR) spectroscopy [4, 5, 14]

Drug-excipient interaction, one of the most essential parameters, was studied before the development of the formulations. The drug polymer and polymer interaction were studied by FTIR spectrometer. Amoxicillin trihydrate and Potassium clavulanate, individually and with all excipients were mixed separately with IR grade KBr. Two percent (w/w) of samples with respect to potassium bromide disc was mixed with dry KBr. The mixture was ground into a fine tablet using an agate mortar and compresses into KBr discs in a hydraulic press at a pressure of 10000 psi or 5.5 metric ton. The pellets were scanned over a wave number range of 4000 to 400 cm^{-1} in Magna IR 750 Series II (Nicolet, USA) FTIR spectroscope. Each KBr disc was scanned and resolution characteristic peaks were recorded.

Formulation of fast dissolving tablets

To formulate fast dissolving tablets, in batches F1 to F4, all excipients were used, whereas in F5 to F8, crospovidone was omitted and for batches, F9 to F12, cross carmellose sodium was omitted. In this tabular presentation, formulations of FDTs were achieved by various concentration ratios of excipients.

Table 1: (A) Formulation of amoxicillin trihydrate and potassium clavulanate dispersible tablets (F1-F6)

S. No.	Ingredients (mg)	Formulation					
		F1	F2	F3	F4	F5	F6
1.	Amoxicillin trihydrate	260	260	260	260	260	260
2.	Potassium clavulanate	40	40	40	40	40	40
3.	Cross carmellose sodium (CCS)	65	65	65	65	65	65
4.	Cross providone	30	35	40	45	-	-
5.	sodium starch glycolate (SSG)	66	66	66	66	66	76
6.	Colloidal silicon dioxide	15	15	15	15	15	15
7.	Talcum	25	25	25	25	25	25
8.	Mannitol	50	50	50	50	50	50
9.	Magnesium stearate	9	9	9	9	9	9
10.	Trusil mango flavour	15	15	15	15	15	15
11.	Aspartame	20	20	20	20	20	20
12.	Micro crystalline cellulose (MCC)	115	110	105	100	145	135
Total (mg)		710	710	710	710	710	710

Where; F= Formulation, Mg= Miligram

Table 1: (B) Formulation of amoxicillin trihydrate and potassium clavulanate dispersible tablets (F7-F12)

S. No.	Ingredients (mg)	Formulation					
		F7	F8	F9	F10	F11	F12
1.	Amoxicillin trihydrate	260	260	260	260	260	260
2.	Potassium clavulanate	40	40	40	40	40	40
3.	Cross carmellose sodium (CCS)	65	65	-	-	-	-
4.	Cross providone	-	-	25	30	35	40
5.	sodium starch glycolate (SSG)	86	96	66	66	66	66
6.	Colloidal silicon dioxide	15	15	15	15	15	15
7.	Talcum	25	25	25	25	25	25
8.	Mannitol	50	50	50	50	50	50
9.	Magnesium stearate	9	9	9	9	9	9
10.	Trusil mango flavour	15	15	15	15	15	15
11.	Aspartame	20	20	20	20	20	20
12.	Micro crystalline cellulose (MCC)	125	115	185	180	175	170
Total (mg)			710	710	710	710	710

Direct compression method [4, 14]

Amoxicillin trihydrate was sifted through #20 mesh. Potassium clavulanate and disintegrants were passed through #40 mesh. Both blends (Kenwood planetary mixer) were mixed. Mixed blend was sifted through sieve no #24 mesh. The remaining amount of aspartame, flavor and talc were sifted through #40 mesh and colour sifted through #60 mesh. Magnesium stearate was sifted through #60 mesh and mixed with the powder blend.

Amoxicillin trihydrate and Potassium clavulanate fast dissolving tablets were prepared by direct compression method according to the formula given in formulation table of fast dissolving tablets. In the present work, 12 formulations of fast dissolving tablets of Amoxicillin trihydrate and Potassium clavulanate (F1 to F12) were prepared using three different super disintegrants, namely; crospovidone, croscarmellose sodium and sodium starch glycolate with different concentrations by direct compression method. The drugs, mannitol and microcrystalline cellulose were mixed uniformly with gentle trituration using mortar and pestle to get a uniform mixture. Required quantity of super disintegrant and aspartame were taken for each specified formulation and mixed with the above mixture. Finally, magnesium stearate and rest excipients were added then mix well. The mixed blend of drug and excipients were compressed using single rotary tablet punching machine to produce tablets, weighing 710 mg each. Before tablet preparation, the mixture blends of all the formulations were subjected to compatibility studies.

Post-formulation studies

Tablets from all the formulation were subjected to following quality control test:

General (physical) appearance [4-9, 14]

The general appearance of tablets, its visual identity, and overall elegance is essential for consumer acceptance. The control of the

general appearance of tablets involves measurement of a number of attributes such as tablet size, shape, colour, presence or absence of an odour, taste and surface texture, physical flaws and consistency and legibility of any identifying marking and hence the parameters were evaluated and compared to standard (IP 2007).

Size and shape [5, 7, 14]

Compressed tablets were examined under the magnifying lens to determine size and shape of tablets.

Tablet thickness and diameter [2, 3, 14]

The thickness and diameter of 10 randomly selected tablets from each formulation were determined in micrometre (mm) using a Vernier calliper (Electro lab India). The average values were calculated. Tablet thickness and diameter is an important characteristic in reproducing appearance and also in counting by using the filling equipment.

Hardness [2, 4, 14]

A tablet was placed between two anvils, the force was applied to the anvils, and the crushing strength that just causes the tablet to break is recorded (in kg/cm²) it was recorded in between 4 to 7. Average of the four determinations was determined and reported. The hardness was tested using "Monsanto hardness tester". The hardness of a tablet is an indication of its strength. During handling and transportation, the tablet should be stable to mechanical stress. The degree of hardness varies with the different manufacture and with the different types of tablets. The force was measured in kg/cm².

Friability test [10, 14, 17]

This in-process quality control test was performed to ensure the ability of tablets to withstand the shocks during processing, handling, transportation, and shipment. Friability is the loss of

weight of tablet in the container/package, due to the removal of fine particles from the surface. It was measured using the USP methods and criteria. Tablet friability was measured using friability tester (Roche friabilator). Permitted friability limit is 1.0%.

Twenty tablets were taken and their weight was determined individually and the average weight of one tablet was determined from the collective weight. In the friabilator, the tablets were exposed to rolling, resulting in free fall of tablets (6 inches) within the chamber of the friabilator. It was rotated at a rate of 25 rpm, after 100 rotations (4 min.), the tablets were taken out from the friabilator, and intact tablets were again weighed collectively.

The percent friability was determined using the following formula;

$$\text{Friability} = (W_1 - W_2) / W_1 \times 100 \text{ ----- (5)}$$

Where, W_1 = weight of the tablet before the test, W_2 = weight of the tablets after test.

Standards: Compressed tablets that loose less than 1.0 % of their weight are generally considered acceptable.

Weight variation test [14, 16-22]

20 tablets were weighed individually and all together. Average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight. The % difference in the weight variation should be within the permissible limits ($\pm 5\%$). The percent deviation was calculated using the following formula;

$$\% \text{ Deviation} = \frac{\text{Individual weight} - \text{Average weight}}{\text{Average weight}} \times 100 \text{ ----- (6)}$$

Any variation in the weight of tablet by any reason leads to either under medication or over medication. So, every tablet in each batch should have a uniform weight. Deviation within the IP permission limit of 5% is allowed as the tablet weight 710 mg.

Content uniformity test [4, 12, 14]

From each batch of prepared tablets, five tablets were collected randomly and powdered. 50 mg of powder, which was equivalent to 10 mg of the drug, was accurately weight and transferred to 100 ml volumetric flask. Then the volume was made up with, pH-6.8 phosphate buffer and shaken or 10 min. to ensure complete

solubility of the drug. Then the solution was filtered. The Same concentration of the standard solution was prepared by dissolving 10 mg of standard solutions in pH-6.8 phosphate buffer. For both the sample and standard solutions absorbance was measured at 245 nm by using double beam spectrophotometer (Shimadzu 1800).

In vitro disintegration time [14, 18-22]

Tablet disintegration is an important step in drug absorption. The test for disintegration was carried out in "Electro lab USP disintegration test apparatus". It consists of 6 glass tubes which are 3 inches long, open at the top, and held against a 10 mesh screen, at the bottom end of the basket rack assembly. This test was carried out at 37 ± 2 °C in 900 ml of distilled water. Six tablets were taken from each batch, and one tablet was introduced in each tube, the disc was placed and basket rack was positioned in 1 liter beaker containing water 37 ± 2 °C. The time taken for the complete disintegration of the tablets with no palatable mass remaining in the apparatus was measured.

Wetting time [12, 14, 22, 24]

A conventional method was used to measure wetting time and capillarity of the orodispersible tablets. The tablet was placed in a Petri dish of 5.5 cm in diameter, containing 10 ml of water at room temperature, and the time for complete wetting was recorded. To check for reproducibility, the measurements were carried out six times and the mean value calculated.

In vitro drug release [4, 12, 14, 18-23]

In vitro drug release rates from different tablets prepared from direct compression method were determined in 900 ml of pH 6.8 phosphate buffer as dissolution media and temperature maintained at 37 ± 0.5 °C with a stirrer rotation speed of 75 rpm using the Dissolution test apparatus (Six basket paddle type apparatus). A 5 ml sample of dissolution medium was withdrawn at 10, 20, 30, 45 min using a cannula and syringe. The sample filtered through whatmann filter paper and suitably diluted and assayed UV Spectrophotometer at 245 nm. An equal volume of fresh medium, which was pre-warmed at 37 °C was replaced into the dissolution medium after each sampling to maintain the constant volume throughout the test. Each dissolution rate test was repeated three times. The sample was taken after various time intervals and absorbance was measured using UV-Spectrophotometer (Shimadzu 1800).

Table 2: Dissolution test parameters of tablets [4, 12, 14]

Apparatus	USP Type II
Volume of medium	900 ml
Temperature	37 ± 0.5 °C
Paddle Speed	75 rpm
Sampling interval time	10,20,30,45 min
Dissolution medium used	6.8 pH phosphate buffer

Comparative study of *in vitro* drug release [14, 16-24]

In vitro drug release studies are critical in determining the rate and extent of drug absorption which in turn affects the therapeutic efficacy of the drug. Absorption of the drug is influenced by its release from the dosage form, its solubility and subsequent permeability into the systemic circulation amongst other factors.

The rate of diffusion of the drug from a tablet is mainly dependent on physicochemical properties of drug and polymers.

However, the mechanisms of release are greatly influenced by the properties of the polymers employed.

The *in vitro* drug release study was carried out in a dissolution apparatus (paddles type) at pH 6.8 phosphate buffer as dissolution media and the temperature maintained at 37 ± 0.5 °C, one tablet is placed in each vessel containing 900 ml of water maintained at temperature 37 °C and rotate paddles with 75

rpm. Collect the sample at 10, 20, 30, 45 min and filter the sample through whattman filter paper and absorbance was measured using UV-Spectrophotometer (Shimadzu 1800). The *in vitro* % drug release of marketed formulation (MP) was compared with *in vitro* % drug release of best formulation of the prepared formulation.

The % drug release profile also compared by plotting a graph between best formulation and marketed formulation, and finally, similarity factor (f_2) was calculated between them.

$$f_2 = 50. \log \{ [1 + (1/n) \sum_{t=1}^n (R_t - T_t)^2]^{-0.5} \times 100 \text{ ----- (7)}$$

Where; f_2 = similarity factor, n = time points,

R_t = percentage drug dissolved at time t for the marketed formulation (MP)

T_t = percentage drug dissolved at time t for the formulation (F4).

RESULTS AND DISCUSSION

Pre-formulation evaluation

Identification and characterization of drugs

Estimation of λ_{max} of amoxicillin trihydrate

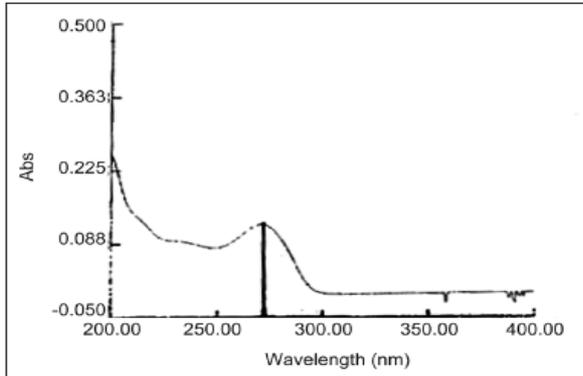


Fig. 1: Maximum wavelength of amoxicillin trihydrate

The λ_{max} of Amoxicillin trihydrate was observed in UV spectrophotometer and the above spectrum suggested the λ_{max} of Amoxicillin trihydrate was found to be 272 nm which provide an appropriate match with the reported λ_{max} 272 nm.

Estimation of λ_{max} of potassium clavulanate

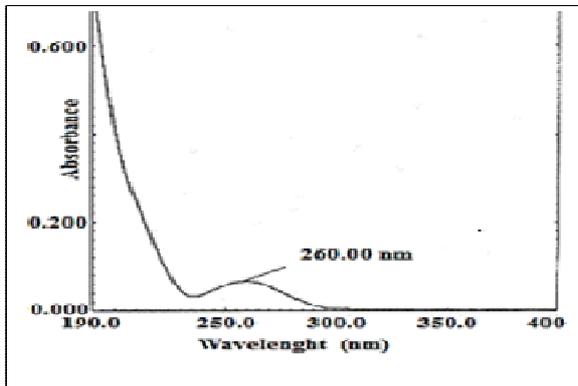


Fig. 2: Maximum wavelength of potassium clavulanate

The λ_{max} of Potassium clavulanate was observed in UV spectrophotometer and the above spectrum suggested the λ_{max} of Potassium clavulanate was found to be 252 nm which provide an appropriate match with the reported λ_{max} 252 nm.

Calibration (standard) curve

Standard curve of amoxicillin trihydrate

Table 3: Absorption of different concentration solutions for standard curve of Amoxicillin trihydrate

S. No.	Concentration ($\mu\text{g/ml}$)	Absorbance at (272 nm)
1	2	0.223
2	4	0.412
3	6	0.593
4	8	0.763
5	10	0.953

Correlation coefficient (R^2)= 0.998, Absorbance $y = 0.093x + 0.021$

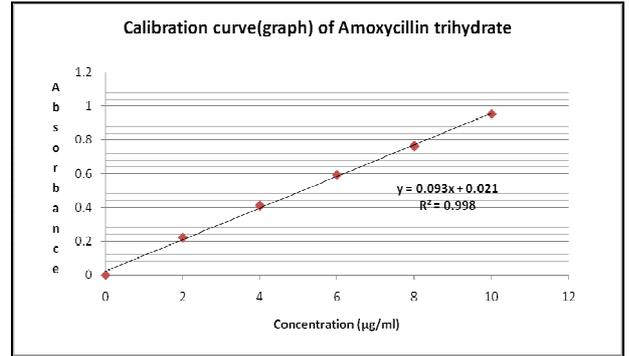


Fig. 3: Calibration (Standard) curve of amoxicillin trihydrate

The absorbance values are listed in table no. (03). The absorbance value showed that it had linear regression and maximum concentration was found to be 10 $\mu\text{g/ml}$. It followed Lambert Beer's law. The standard plot of Amoxicillin trihydrate is shown in fig. No. (03). The absorbance of Amoxicillin trihydrate solutions was recorded at λ_{max} 272 nm using double beam UV-Visible Spectrophotometer. A standard graph was plotted between the concentration (on X-axis) and absorbance (on Y-axis).

Standard curve of potassium clavulanate

Table 4: Absorption of different concentration solutions for standard curve of Potassium clavulanate

S. No.	Concentration ($\mu\text{g/ml}$)	Absorbance at (252 nm)
1	2	0.212
2	4	0.392
3	6	0.571
4	8	0.723
5	10	0.911

Correlation coefficient (R^2)= 0.998, Absorbance $y = 0.088x + 0.016$

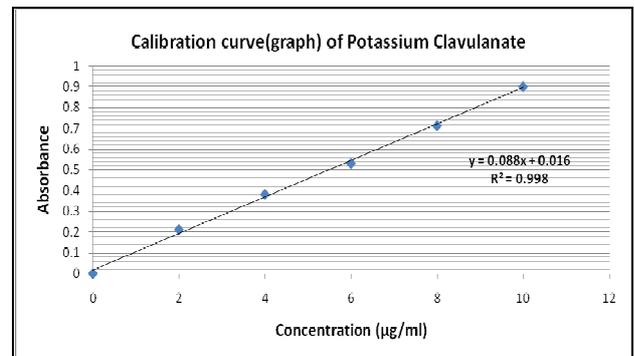


Fig. 4: Calibration (Standard) curve of potassium clavulanate

The absorbance values are listed in table no. (04). The absorbance value showed that linear regression and maximum concentration found to be 10 $\mu\text{g/ml}$. It followed Lambert Beer's law. The standard plot of Potassium clavulanate was shown in fig. No. (04). The absorbance of Potassium clavulanate solutions was recorded at λ_{max} 258 nm using double beam UV-Visible Spectrophotometer. A standard graph was plotted between the concentration (on X-axis) and absorbance (on Y-axis).

IR spectra of drug and excipients

Drug excipients interaction was checked out by comparing the IR spectra of pure drug Amoxicillin trihydrate, Potassium clavulanate and IR spectra of the physical mixture (excipients).

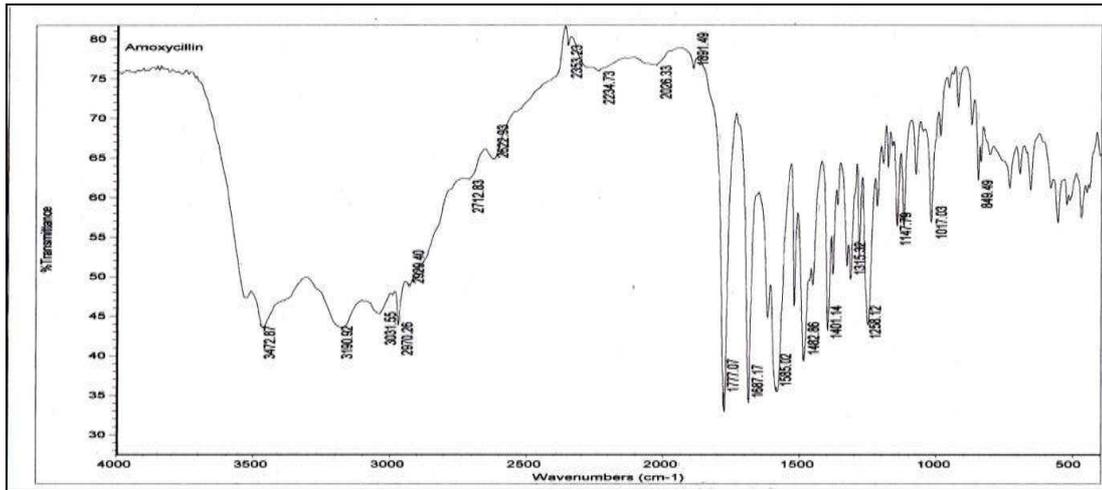


Fig. 5: IR spectra of amoxicillin trihydrate

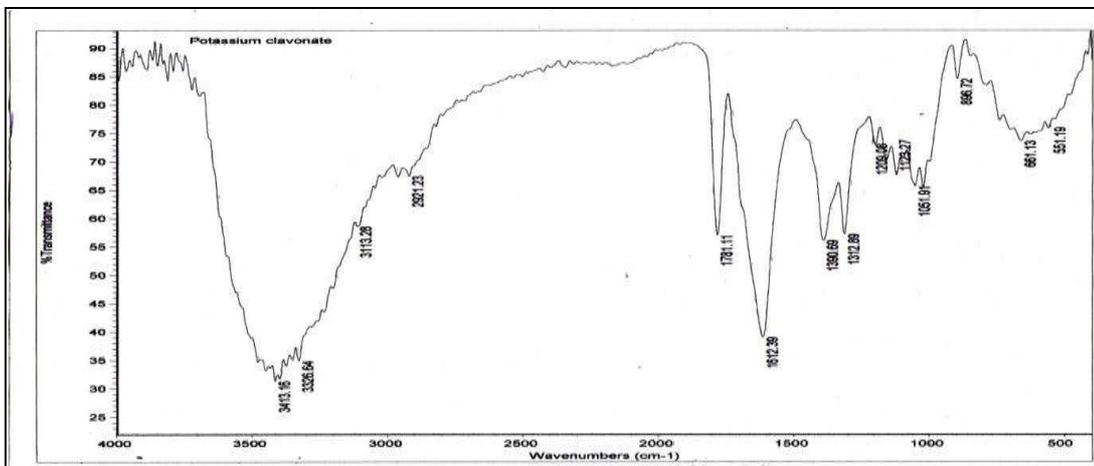


Fig. 6: IR spectra of potassium clavonate

FTIR-spectroscopy shows the interaction between the molecules at the level of functional groups. Here drug-excipient interaction was studied using FTIR-spectroscopy. Between 3200 cm and 2800 cm and between 1800 cm and 1000 cm wave 1 numbers, variations at transmission spectroscopy data were noted. Alkenyl (-C=C-) (3020 cm-1-1-1-1-1 3100 cm), amide (-NH) (1000 cm-1250 cm) ketonyl (C=O) (1710 cm-1720 cm),-1-1 phenolic (-OH) (970 cm-1250 cm)

stretches are mainly responsible for those regions. Drug sample and standard drug-IR spectra of Amoxicillin trihydrate were compared, and both sample and standard drug-IR spectra indicate no significant difference in characteristic peak. Drug sample and standard drug-IR spectra of Potassium clavonate were compared, and both sample and standard drug-IR spectra indicate no significant difference in characteristic peak.

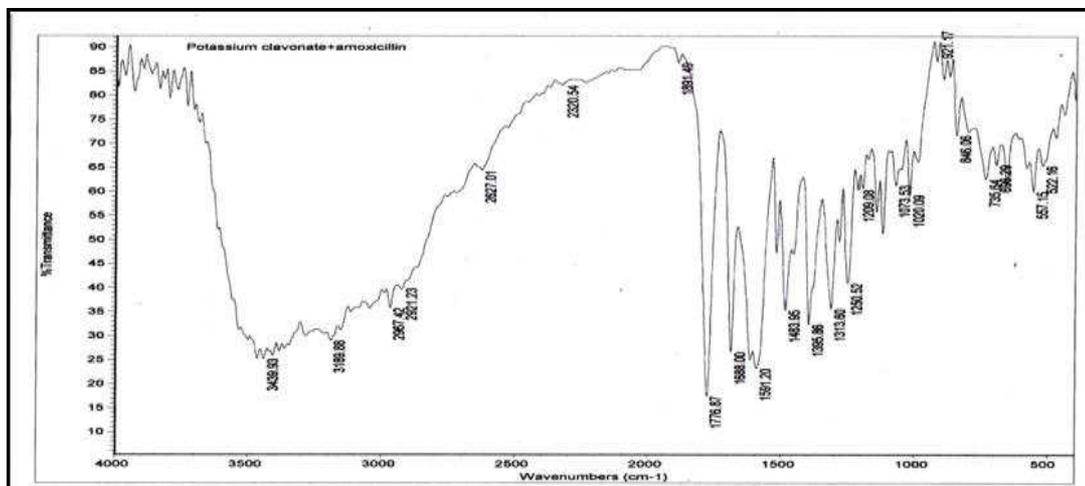


Fig. 7: IR spectra of amoxicillin trihydrate and potassium clavonate drug samples

Fig. (07) was shown an increase in the spectra at 1080 and 800 nm, which were the -NH and C=O spectra. This data support the prediction that there is a formation of hydrogen bonding between NH/-C=O site of Potassium clavulanate with the Amoxicillin trihydrate. Compatibility of the drug with excipients was determined by FTIR

spectral analysis; this study was carried out to detect any changes on chemical constitution of the drug after combined it with the excipients. IR spectra indicate no significant difference in a characteristic peak at wave numbers of the drug in the presence of the excipient. Thus IR spectra indicated no drug-excipient interaction.

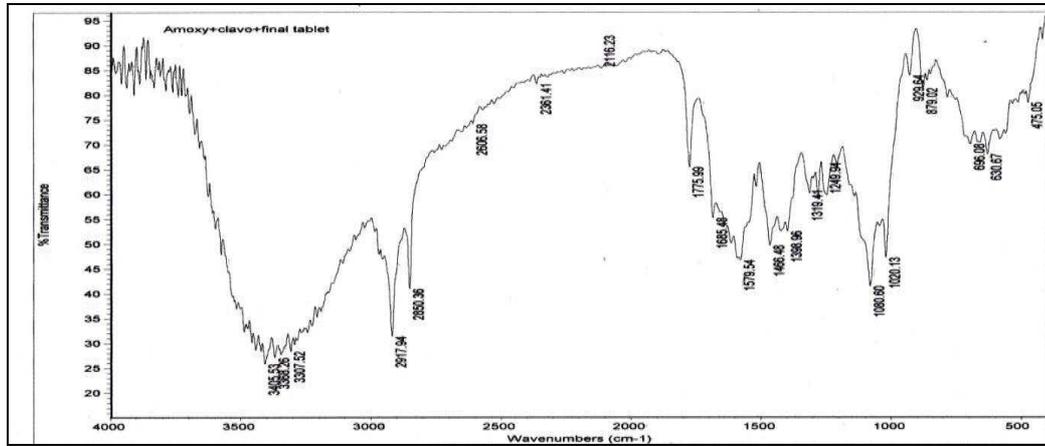


Fig. 8: IR spectra of amoxicillin trihydrate and Potassium clavulanate and all excipients

Solubility

Amoxicillin trihydrate was slightly soluble in water, methanol, 0.1N HCL, pH 6.8 phosphate buffer. Potassium clavulanate was freely soluble in water, soluble in methanol and also 0.1N HCL and pH 6.8 phosphate buffers.

Flow properties evaluation

Bulk density results were between 0.460–0.471 gm/ml. The results of all batches were within the IP limit. Batch F4 have shown good flow property. Tapped density results were between 0.530–0.538 gm/ml. The results of all batches were within the IP (2007) limits. Batch F4 have shown good flow property. The compressibility flowability correlation data indicated a fairly good flowability of the

powder blend. Using bulk density and tapped density data the compressibility index was calculated. The compressibility index was found to be 9.77-16.55. The powder blends of all the formulations had hausner's ratio ranging from 1.10 to 1.16 indicating good flowability.

The good flowability of the powder blend was also evidenced with the angle of repose (range of 22.2–22.7), which is below 400 indicating good flowability. Evaluation of powder blends was determined successfully. The results of carr's index and the Hausner's ratio of all batches were within IP (2007) limits. The angle of repose was also successfully determined. Batch F4 have shown good flow property and taken as the final formulation from all twelve formulations.

Table 5: (A) Characterization of powder blends (F1-F6)

S. No.	Name of test (Avg.)	Formulation					
		F1	F2	F3	F4	F5	F6
1.	Bulk density (gm/ml)	0.460 ±0.01	0.470 ±0.02	0.460 ±0.02	0.471 ±0.01	0.465 ±0.03	0.462 ±0.02
2.	Tapped dens-ity (gm/ml)	0.532 ±0.03	0.522 ±0.04	0.532 ±0.06	0.538 ±0.03	0.536 ±0.05	0.522 ±0.03
3.	Carr's index	13.53 ±0.16	9.77 ±0.17	13.38 ±0.19	9.77 ±0.15	13.29 ±0.14	13.2 ±0.16
4.	Hausners Ratio	1.15 ±0.17	1.10 ±0.12	1.15 ±0.22	1.16 ±0.21	1.25 ±0.19	1.16 ±0.25
5.	Angle of repo-se (degree)	22.4 ±0.22	22.3 ±0.26	22.2 ±0.32	22.7 ±0.22	22.6 ±0.27	22.4 ±0.35

±SD, n=6.

Table 5: (B) Characterization of powder blends (F7-F12)

S. No.	Name of the test (Avg.)	Formulation					
		F7	F8	F9	F10	F11	F12
1.	Bulk density (gm/ml)	0.460 ±0.01	0.450 ±0.02	0.465 ±0.02	0.455 ±0.01	0.460 ±0.01	0.470 ±0.02
2.	Tapped dens-ity (gm/ml)	0.532 ±0.04	0.535 ±0.05	0.535 ±0.06	0.537 ±0.04	0.532 ±0.03	0.536 ±0.04
3.	Carr's index	13.55 ±0.15	15.82 ±0.17	16.17 ±0.17	16.55 ±0.16	13.08 ±0.16	13.66 ±0.15
4.	Hausners Ratio	1.15 ±0.26	1.17 ±0.28	1.16 ±0.25	1.14 ±0.28	1.15 ±0.29	1.13 ±0.23
5.	Angle of repo-se (degree)	22.6 ±0.38	22.5 ±0.35	22.4 ±0.28	22.3 ±0.24	22.5 ±0.39	22.6 ±0.42

±SD, n=6.

Post-formulation evaluation**Evaluation of tablet formulations**

Amoxicillin trihydrate and Potassium clavulanate FDTs general (physical) appearance were observed odour; odourless, taste; bitter less and color; white. It was compared to standard specification IP (2007) and those were not different from the color, odour, and taste which suggested its equivalence to the specifications.

The average weights of 20 tablets were calculated for each formulation, and it varies from 706 to 710 mg which complied with the official limit of the IP (2007). Formulation F4 has shown no weight variation. All the formulations have an average hardness in between 4.16 to 5.45 kg/cm² which was found to be acceptable; because these formulations have to be disintegrated on the tongue between 25 second to 50 second. So excess of hardness was not favored for these formulations. The hardness for formulation F1 (5.45 kg/cm²) was found to be highest of all formulations and for F12 (4.16 Kg/cm²) was found to be least and marketed formulation

(MP) which shown (4.97 Kg/cm²) values respectively for the above parameters and the results were shown in table no. (06).

The average percentage friability for all the formulations were between 0.22 to 0.60 % which was found to be within the IP (2007) limit (i.e. maximum 1%). From all prepared formulations maximum friability was 0.55% and the minimum friability 0.22% observed for F11 and F4 respectively, and marketed formulation (MP) which shown 0.60 % values respectively for the above parameters and the results were shown in table no. (06). The average length for all the tablets formulations was between 15.1 to 15.9 mm.

Examination of all batch showed flat circular shape of tablets with no cracks. All the dispersible tablet formulations were evaluated for their thickness using Vernier calipers and the results were shown in table no. (06). The thicknesses of all the formulations were within the range of 5.14 to 5.20 mm. Formulation batch F4 has shown good thickness result. The ranges of average width for all formulation were shown between 08.15 to 08.20 mm.

Table 6: (A) Post compression studies of formulation F1 to F12 and MP

Formula-tions	Parameters				
	Weight Variation (mg)	Hardness (Kg/cm ²)	Friability (%)	Length (mm)	Thickness (mm)
F1	708±1.09	5.45±0.15	0.24±0.05	15.6±1.80	5.14±0.21
F2	707±2.01	5.11±0.17	0.25±0.06	15.8±1.20	5.17±0.26
F3	709±1.05	5.20±0.19	0.24±0.07	15.7±1.40	5.15±0.24
F4	710±0.09	5.10±0.11	0.22±0.02	15.9±1.50	5.16±0.21
F5	707±2.09	4.22±0.18	0.34±0.08	15.1±1.10	5.18±0.28
F6	708±1.01	4.58±0.20	0.41±0.06	15.3±1.30	5.15±0.27
F7	706±2.02	5.11±0.21	0.39±0.04	15.5±1.80	5.16±0.23
F8	707±1.49	4.44±0.15	0.44±0.03	15.4±1.60	5.14±0.25
F9	706±2.03	5.05±0.17	0.35±0.02	15.5±2.01	5.16±0.21
F10	707±2.06	4.73±0.18	0.36±0.03	15.3±2.02	5.15±0.28
F11	708±1.01	4.77±0.13	0.54±0.06	15.5±1.80	5.17±0.22
F12	709±1.01	4.16±0.15	0.45±0.06	15.2±2.80	5.16±0.29
MP	709±1.01	4.97±0.15	0.60±0.06	15.2±1.90	5.20±0.29

±SD, n=6. MP= Marketed formulation (Preparation).

The values of FDTs disintegration time have found in the range of 25 to 50 second. Batch F1 to F4 were shown better disintegration time with three super disintegrants (cross carmellose sodium, sodium starch glycolate and crospovidone). The *in vitro* disintegration time for formulation F4 was 25 seconds and highest disintegration time was found to be marketed formulation was 53 seconds. The average wetting time for all the formulations was in the range of 55 to 65 seconds. The maximum wetting time of 65 second and minimum wetting time

of 28 seconds have shown by F5 and F4 respectively and marketed preparation which shows 62 seconds respectively for the above parameters and the results were shown in table no. (06). The amount of drug present in all the formulations varies from 95.4 to 99.5 % w/w which is within the official limit of IP (2007) i.e. 90-110 %. Thus all the formulations were found to be complying with the standards given in IP (2007). Formulations F4 and MP (marketed preparation) have shown 99.5%w/w and 96.4%w/w respectively uniformity of drug content.

Table 6: (B) Post compression studies of formulation F1 to F12 and MP

Formula-tions	Parameters				
	Width (mm)	Disintegration time(Sec)	Wetting time(sec)	Uniformity of dispersion	Assay (%) Amoxy. tri. and Pot. clav
F1	8.17±1.50	45±0.15	58±0.42	Pass	97.7
F2	8.18±1.56	42±0.17	62±0.44	Pass	98.1
F3	8.19±1.70	40±0.19	61±0.47	Pass	97.6
F4	8.16±1.20	25±0.11	55±0.37	Pass	99.5
F5	8.18±1.80	37±0.18	65±0.49	Pass	96.8
F6	8.15±2.20	39±0.20	62±0.42	Pass	95.7
F7	8.18±1.91	40±0.21	64±0.46	Pass	96.5
F8	8.19±1.53	35±0.15	63±0.41	Pass	95.4
F9	8.15±1.79	38±0.17	62±0.46	Pass	95.9
F10	8.19±1.88	33±0.18	63±0.45	Pass	96.7
F11	8.15±1.85	35±0.13	60±0.44	Pass	95.8
F12	8.17±2.10	40±0.15	64±0.43	Pass	96.5
MP	8.20±2.18	50±0.15	62±0.44	Pass	96.4

±SD, n=6, Amoxy. tri. and Pot. clav. = Amoxicillin trihydrate and Potassium clavulanate.

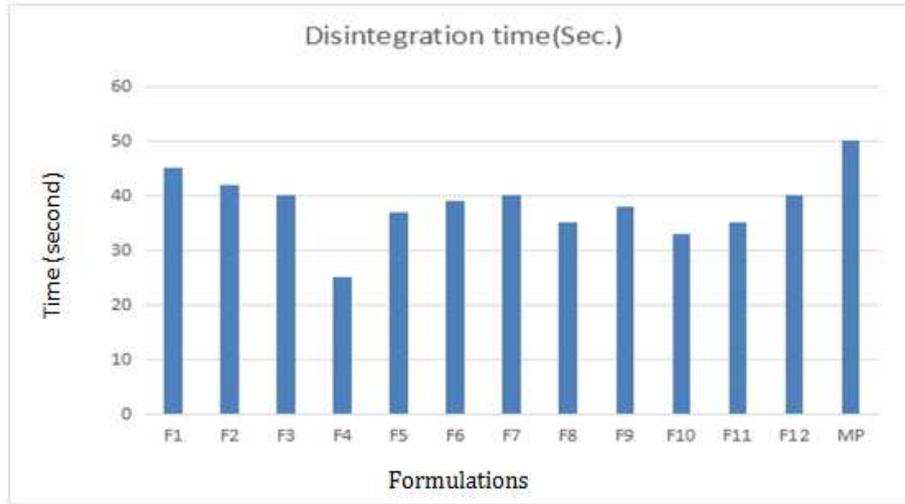


Fig. 9: Comparison of disintegration time of formulations F1 to F12 and marketed formulation (MP)

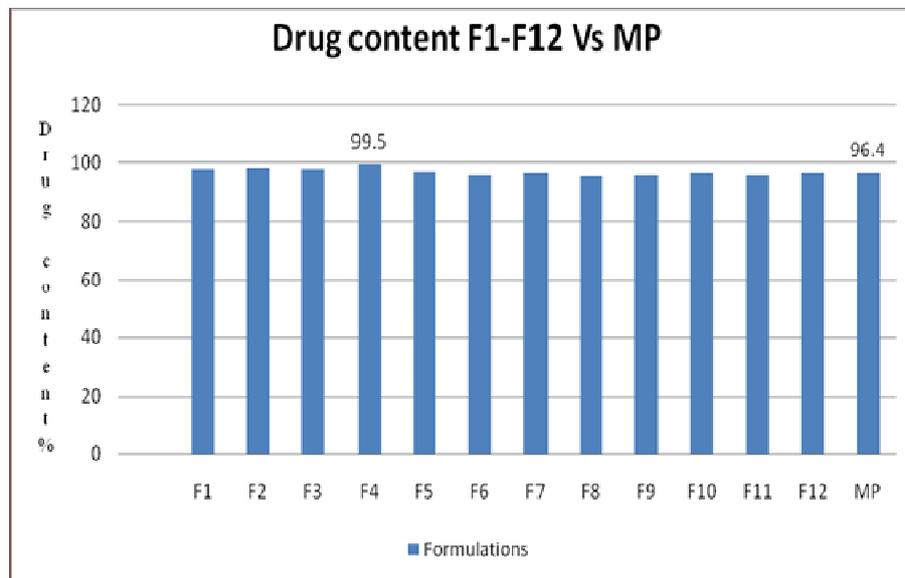


Fig. 10: Drug content of formulation F1-F4 Vs MP (Marketed formulation)

Table 7: *In vitro* dissolution study of amoxicillin trihydrate and potassium clavulanate formulations (F1-F12)

Formulation	% Drug release (Avg)			
	10 Min	20 Min	30 Min	45 Min
F1	76.732±0.49	86.73±0.69	96.732±0.59	97.922±0.33
F2	78.433±0.59	92.25±0.84	95.125±0.62	98.185±0.37
F3	78.433±0.66	89.34±0.82	96.222±0.63	97.921±0.37
F4	80.732±0.44	95.25±0.86	98.125±0.61	99.685±0.34
F5	50.485±0.54	61.24±0.81	65.182±0.67	78.764±0.35
F6	63.654±0.58	74.42±0.86	80.678±0.77	88.696±0.34
F7	66.658±0.58	77.42±0.88	82.687±0.78	89.696±0.39
F8	67.554±0.52	77.22±0.83	84.678±0.91	91.696±0.32
F9	66.45±0.56	78.21±0.74	88.76±0.89	94.69±0.37
F10	67.65±0.54	73.42±0.72	85.67±0.69	95.69±0.36
F11	68.65±0.34	78.52±0.81	87.95±0.79	96.69±0.38
F12	70.65±0.54	78.72±0.84	88.34±0.76	97.91±0.37

±SD, n=6.

The results of the *In vitro* dissolution studies were shown in table no. (07), for formulation F1 to F12. *In vitro* dissolution test reveals the release increase from 50% to a maximum of almost 99% from 10 min to 45 min for Amoxicillin trihydrate and Potassium clavulanate fast dissolving tablets.

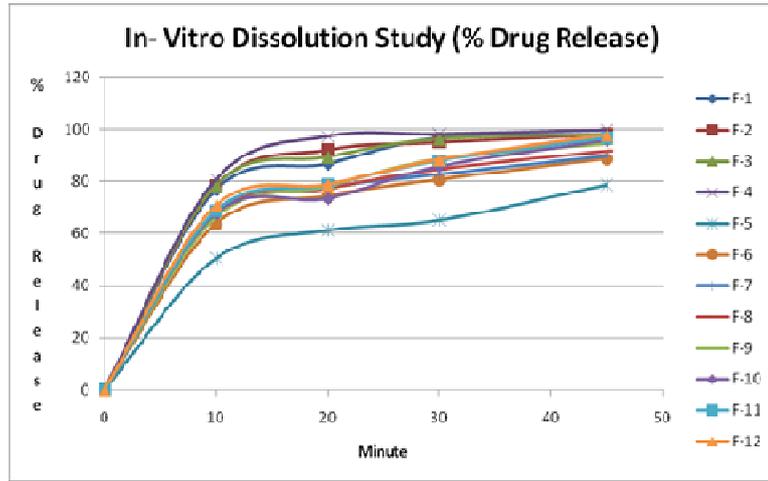


Fig. 11: *In vitro* dissolution study (%drug release) of amoxycillin trihydrate and potassium clavulanate Formulations (F1-F12)

All the fast dissolving tablet formulations were evaluated for their *in vitro* drug release by six basket paddle type apparatus and the results are shown in fig. no. (11). The maximum drug release of

99.6% was obtained from formulation F4. The average drug release immediately after dispersion for all the formulations was in the range of 50.48% to 99.6%.

Table 8: *In vitro* dissolution (%drug release) compare between F4 and MP

Formulation	Dissolution			
	10min	20min	30min	45min
Formulation (F4)	80.732±0.78	96.251±0.84	98.125±0.88	99.685±0.75
Marketed formulation	78.274±0.72	86.111±0.90	92.211±0.93	96.807±0.73

±SD, n=6, MP =Marketed formulation, F= formulation, Min. = Min.

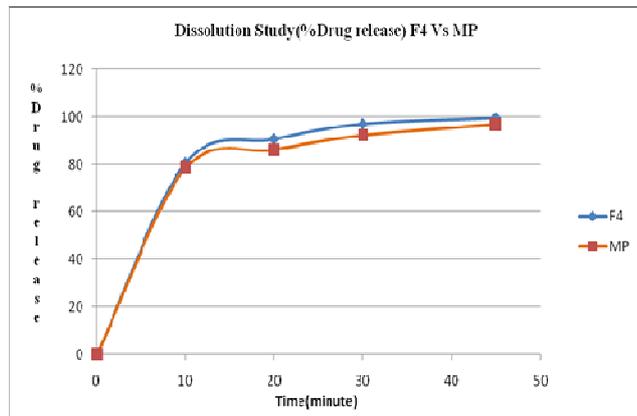


Fig. 12: Comparison of dissolution property between MP (marketed formulation) and formulation (F4)

Formulation F4 *in-vitro* drug release compared with the marketed formulation *in vitro* drug release. Formulation F4 has shown comparable *in vitro* drug release with marketed formulation (MP).

Similarity factor

Table 9: Similarity factor (f_2) F4 Vs MP

Similarity factor (f_2)	Dissolution			
	10Min.	20Min.	30Min.	45Min.
Formulation (F4)	76.2	81.5	86.3	93.1
Marketed formulation	72.2	78.1	84.1	86.3

Similar, when $f_2 = 50-100$

The results obtained for similarity factors are shown in table no. (09). Formulation F4 and MP (marketed formulation) within the specified range of similarity (72-94).

The dissolution of formulation F4 and MP (marketed formulation) samples were subjected to the same conditions hence adequate comparison can be made. The lower acceptable f_2 value obtained in a test ($f_2 = 50$) corresponds to 10% average absolute difference between a reference product and a test product at each time point.

Formulation batch F4 and MP (marketed formulation) have shown similarity in their dissolution profile.

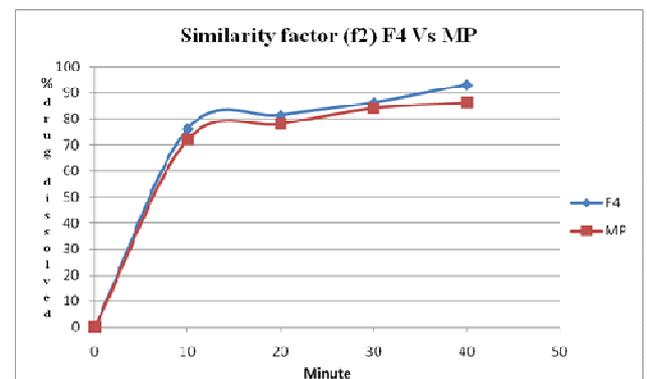


Fig. 13: Similarity factor (f_2) F4 Vs MP

SUMMARY AND CONCLUSION

The compatibility parameters evaluation of both the drugs (Amoxycillin trihydrate and Potassium clavulanate) and excipients were done by FTIR method and no interaction found between drugs and excipients. The blend ready for compression was evaluated for

bulk density, tapped density, carr's index, hausner's ratio, the angle of repose. It was found that blend had carr's index and hausner's ratio was in the acceptable limit, which indicates that blend was having excellent flow property and compressibility property. Fast dissolving tablets of Amoxicillin trihydrate and Potassium clavulanate were prepared by direct compression method using cross carmellose sodium, sodium starch glycolate and crospovidone super disintegrant. Tablets were evaluated for hardness, friability, disintegration time, uniformity of dispersion, assay and dissolution study. Tablets having uniform weight, hardness and friability data indicate the good mechanical resistance of the tablets. The tablets were evaluated for length, thickness and width and it was found to be within the IP (2007) limits and also calculated similarity (f_2) factor between best formulation F4 and marketed formulation.

Disintegration time was also found within IP (2007) limit. The batch F4 shown best disintegration time compared to disintegration time of marketed formulation. The tablets also evaluated for the weight variation that found to be within the IP (2007) limits. Fast dissolving tablets of Amoxicillin trihydrate and Potassium clavulanate formulation F4 shown better *in vitro* dissolution of the drug compared to marketed formulation. The present research works found comparable with a marketed formulation for all evaluation parameters of fast dissolving tablets. The results obtained for similarity factors of formulation batch F4 and MP (marketed formulation) has shown similarity in their dissolution profile. From the present study, it was revealed that the approaches and techniques employed in formulation and development of fast dissolving tablets were simple, feasible and has potential commercial importance. From the results, it can be concluded that formulation batch-F4 shown the optimum and effective result. Hence, a combination of Amoxicillin trihydrate and Potassium clavulanate can be successfully formulated as fast dissolving tablets in new concentration (ratio) of drugs and excipients.

As a scope for further studies, packaging parameters, stability study of the formulation can be performed. This will help to discover if any incompatibility observed during packaging and stability studies in this new ratio of drugs and excipients. Along with this, the pharmacokinetics properties of the formulation can be evaluated by *In vivo* study in humans, to establish the *In vitro In vivo* correlation (IVIVC) database.

CONFLICT OF INTERESTS

Declare none

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How to cite this article

Ashish Masih, Ajay Kumar Tiwari. Formulation and evaluation of fast dissolving tablets of amoxicillin trihydrate and potassium clavulanate. *Int J Curr Pharm Res* 2017;9(2):48-58.