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DEVELOPMENT AND EVALUATION OF BILAYER TABLET OF CEFUROXIME AXETIL AND POTASSIUM CLAVULANATE.

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ABSTRACT

The present research was carried out with the aim of developing bilayer tablet to improve therapeutic efficacy with optimum drug plasma level which contains two antibiotics i.e. Cefuroxime axetil and Potassium clavulanate. Cefuroxime axetil is an orally active 2nd generation cephalosporin. Clavulanic acid is β lactamase inhibitor. This formulation comprises of Cefuroxime axetil as immediate releasing layer using superdisintegrant Crosscarmellose and Potassium clavulanate as extended release layer using different concentrations of HPMC K4M. Both layer compositions were prepared separately by dry granulation. Bilayer tablet after compression were film coated and final bilayered tablets were evaluated for various physical parameters, *in vitro* dissolution profile and short term stability. All the values found to be within limits. *In vitro* dissolution kinetics followed the Higuchi model via diffusion mechanism after initial immediate release. Stability studies were conducted indicating the integrity of optimized formulation i.e. physical appearance, drug content and *in vitro* dissolution profile. From the results of present study it was concluded that Cefuroxime Axetil-Potassium clavulanate bilayer tablet can be successfully developed.

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Key Words

Bilayer tablets, Cefuroxime axetil, HPMC K4M, Potassium clavulanate

INTRODUCTION

Oral administration of drug is most common and preferred route because of the ease of administration, patient compliance and economic aspect of manufacturing. Among the oral dosage forms tablets of various different types are the most common.¹ Fixed dose combination (FDC) therapy has various advantages over conventional monotherapy such as simpler dosage schedule leading to improved patient compliance and therefore improved treatment outcomes, reduced side effects, reduced development of resistance in the case of antimicrobials and potentially lower cost of manufacturing, handling, packing and shipping compared the costs of producing separate products. Delivery systems for designing FDC are as follows.²

- Multilayer tablet e.g. Bilayer tablet, trilayer tablet
- Multiple Unit Particulate System
- Multiple Unit Bead/coating System
- Multicompartment capsules e.g. Capsules within capsules
- Tablet in tablet technology
- Inlay technology

Bilayer tablet is a formulation of two or more active pharmaceutical ingredients (API) combined in a single dosage form available in certain fixed doses. Chemical incompatibilities in the formulation is avoided by physical separation of API and the same approach allows to design different release profile for example immediate release and extended release from the same dosage form.^{3,4}

Cefuroxime axetil (CA), prodrug of 2nd generation cephalosporin Cefuroxime, possesses 1-acetoxy-ethyl group that increases absorption of Cefuroxime from GIT.⁵ Bioavailability is greatly decreased (<50 %) in intestine because CA is rapidly hydrolyzed by non specific esterases in intestinal mucosa releasing Cefuroxime which is poorly absorbed. Therefore CA if not immediately released from dosage form misses the absorption window in the upper GI tract and remains unabsorbed causing high level of antibiotic enteric colon causing antibiotic associated colitis.⁶ Another object was to administer Cefuroxime as CA by oral route to solve various problems which is caused by injectable form of the antibiotic for example chances of overdose,

Belonephobia (the fear of needle and injection), risk of infection (if needle shared or not properly sterilized) and strict need of asepsis during administration. Therefore CA was formulated as immediate releasing layer in bilayer tablet with superdisintegrant Crosscarmellose.

Extended release layer of bilayer tablet is of β lactamase inhibitor Clavulanic acid which produced from *Streptomyces clavuligerus*. Clavulanic acid is incorporated in form of Potassium clavulanate which is a suicide inhibitor, its covalent bonding to a serine residue in the active site of the β lactamase results in the restructuring of the Potassium clavulanate molecule, creating a much more reactive species that is attacked by another amino acid in the active site, which permanently inactivating the enzyme thus preventing the destruction of Cefuroxime that is a substrate for this enzyme. This inhibition restores the antimicrobial activity of β -lactam antibiotics against β lactamase-secreting bacteria.⁷ Different concentrations of HPMC K4M were used to formulate extended release layer of Potassium clavulanate.

The rationale for combination therapy is to provide a solution for treatment of bacterial infections caused by β lactam resistant bacteria. Although Clavulanic acid does have some degree of bacterial activity, its principal role is as a β lactamase inhibitor. β lactam antibiotics, such as the cephalosporins, act by disrupting the development of bacterial cell walls thus causing the disintegration of the bacteria. However, some bacteria acquire the genes to produce enzymes which inactivate this mode of action - so called β lactamases drastically reducing the efficacy of this class of antibiotics. Clavulanic acid has a similar structure to the β lactam antibiotics but binds irreversibly to the β lactamase enzymes. Thus, Clavulanic acid used in combination with the β lactam antibiotics, has become one of the most prescribed antibiotics prolonging the effective life of antibiotics.^{8, 9, 10}

The objective of the present research work was to develop a combination drug therapy of two antibiotics having different mechanisms of action thereby having synergistic effect against microbial infections and to minimize dose dependent side effects.

MATERIAL AND METHODS**Material:**

Cefuroxime axetil and Potassium clavulanate were obtained as gift sample from Varun Medico Lab Pvt. Ltd, India. All the materials used were of analytical grade and procured from commercial sources.

Preparation of Bilayer tablet:^{1,2,3,14}

Cefuroxime axetil and Potassium clavulanate bilayer tablet were prepared by dry granulation process. Cefuroxime axetil granules were formulated as immediate releasing layer and Potassium clavulanate granules were formulated as extended release layer. This preparation consists of four steps.

Table 1 Composition for Cefuroxime axetil layer

| Ingredient | Formulation (mg/tablet) |
|---|-------------------------|
| | (C1) |
| Cefuroxime Axetil (equivalent to Cefuroxime 500mg) | 620 |
| Croscarmellose sodium | 40 |
| MCC | 16 |
| MCC (PH 200) | 30 |
| 1-vinyl 2-pyrrolidinone | 25 |
| Aerosil | 9 |
| Talc | 4 |
| Magnesium stearate | 6 |

Step 1: Preparation of Cefuroxime axetil granules:

All required ingredients were sieved and weighed according to the composition formula mentioned in table 1. All the ingredients excluding aerosil, half quantity of magnesium stearate, Croscarmellose sodium were mixed geometrically and blended together and compacted using a roller compactor, the flakes or slugged material milled through an oscillating granulator to get suitable granules. The resultant granules blended with remaining excipients.

Step 2: Preparation of Potassium clavulanate granules:

Three different Potassium clavulanate formulations were prepared using different concentrations of HPMC K4M. All required ingredients were sieved and weighed according to the formula mentioned in table 2. In Each formulation all ingredients excluding half quantity aerosil, magnesium stearate and 1 vinyl 2-pyrrolidinone

were mixed geometrically, blended together and compacted using a suitable roller compactor, the flakes or slugged material milled through an oscillating granulator to get suitable granule. The resultant granules were blended with remaining excipients to obtain final blends for Potassium clavulanate layer.

Table 2 Composition for Potassium clavulanate layer

| Ingredient | Formulation (mg/tablet) | | |
|--|-------------------------|------|-------|
| | F1 | F2 | F3 |
| Potassium clavulanate (equivalent to Clavulanic acid 125 mg) | 308 | 308 | 308 |
| HPMC | 9.0 | 10.0 | 10.66 |
| MCC | 61 | 61 | 61 |
| MCC (PH200) | 40 | 40 | 40 |
| 1-venyl 2-pyrrolidinone | 20 | 20 | 20 |
| Aerosil | 3.34 | 3.34 | 3.34 |
| Talc | 2 | 2 | 2 |
| Magnesium stearate | 5 | 5 | 5 |

Step 3: Compression

The tablets were compressed by using the double sided tablet press. Accurately weighed Cefuroxime axetil granules are initially introduced and slightly pre-compression was made so that layer was uniformly distributed after which accurately weighed Potassium clavulanate granules were added and final compression was made till desired hardness is attained.

Step 4: Coating

Avoidance of absorbing moisture from Potassium clavulanate is done by film coating of formulated bilayer core tablet with moist shield material. The film forming composition were prepared by dispersing the ingredients in solvent mixture and filtered. The filtered solution was sprayed over previously coated tablet in a coating pan. Target weight gain 1.5-2.0%

Table 3 Composition of film coating mixture.

| Composition | Amount (mg) |
|--------------------|-------------|
| HPMC E15 | 12.5 |
| Dibutyl phthalate | 3.33 |
| Talc | 0.93 |
| Titanium dioxide | 5 |
| Isopropyl alcohol | 116.66 |
| Methylene chloride | 350 |

PHYSICOCHEMICAL EVALUATION OF TABLET:**Thickness**

10 tablets were evaluated for thickness in millimeters by using vernier caliper.

Weight variation

20 tablets were weighed on analytical balance. The average weight and percentage variation were calculated.

Hardness

Monsanto hardness tester was used to determine the hardness of 6 tablets. The average pressure applied for crushing tablet was reported.

Friability

20 tablets were weighed after dusting & then placed in a Roche Friabilator, rotated at 25 rpm for 4 minutes. The tablets were weighed again after dusting. Percentage of weight loss was calculated to determine friability.

Uniformity of dosage units

Uniformity of dosage form was evaluated as per USP requirement <905> for content uniformity.¹¹ The batch meets the requirement if the amount of the active ingredient in each of the 10 tested tablets lies within the range of 85% to 115% of label claim.

Dissolution studies

In vitro drug release of Cefuroxime axetil was determined using a USP dissolution Apparatus type II (paddle type) in 900 ml of 0.07 N HCL solution with agitation speed 55 rpm. Temperature was maintained at $37 \pm 0.5^\circ\text{C}$. Sample was withdrawn at 15, 30, 45 and 60 minutes filtered through Whattman filter paper and equal volume of fresh dissolution medium was replaced. After suitable dilution analyzed by UV spectrometry at 278 nm.¹² The percentage of Cefuroxime axetil released was calculated.

In vitro release of Potassium clavulanate was determined using USP dissolution Apparatus II (paddle type) at 75 rpm in 900 ml of distilled water. The temperature was maintained at $37 \pm 0.5^\circ\text{C}$. Sample was withdrawn at time interval of 15, 30, 45, 60, Samples were diluted and analyzed for Potassium clavulanate by HPLC method.¹³

HPLC conditions

Apparatus : High Pressure Liquid
Chromatography
Column : C18 250×4.6 mm, 5 μm (Hypersil
BDS)
Flow Rate : 2 ml/min
Wavelength : 220 nm

Injection volume : 20 μl

Diluent : pH 4.4 Sodium phosphate buffer

Detector : PDA (Photodiode Array)

Mobile phase : Mixture of pH 4.4 Sodium phosphate buffer and methanol (95:5), filter and degas.

Buffer : pH 4.4 Sodium phosphate buffer

Dissolve 7.8 g of monobasic sodium phosphate in 900 mL of water, adjust with phosphoric acid or 10 N sodium hydroxide to a pH of 4.4 ; 0.1, dilute with water to 1000 mL, and mix.

Standard solution:

Dissolve accurately weighed quantities of Potassium clavulanate working standard in water to obtain a solution having known concentrations of about 0.2 mg per mL. Filter this solution using 0.45 μm membrane.

Sample solution:

10 ml of sample was withdrawn at each time interval and it was filter using 0.45 μm membrane. This 10ml withdrawn sample was diluted to 50ml with the dissolution media. Filter this solution using 0.45 μm membrane.

Drug content:

Cefuroxime axetil was determined by UV spectrometry and Clavulanic acid was determined by HPLC method.

Stability studies

The stability study was carried out according to ICH and WHO guidelines. The optimized formulation was subjected to stability at 40(+)-2 degree C and 75(+)-5 RH for period of one month. After which tablet sample was analyzed for physical characteristics and drug release profile.

RESULTS AND DISCUSSION:

The bilayer tablets were prepared by dry granulation technique. Three formulations-C1F1, C1F2 and C1F3 were prepared using different concentration of HPMC K4M and evaluated. The preformulation data obtained were within prescribed limit and indicates good flow property. After compression tablets were evaluated and results of tests are shown in Table 5. Tablets of all formulation demonstrated good thickness, friability, hardness, and disintegration time. Batches of all the formulations passed weight variation test since the percentage of weight variation was within prescribed pharmacopoeial limit. During short term stability studies

formulations did not show any drug-drug and drug excipients interactions, and therefore it was concluded the excipients which have been selected for the formulation were compatible with the drugs. Among all the formulation C1F3 has shown good hardness, low friability, optimum disintegration time also percentage

of drug release was 97.1 to 97.25 %. From the results of evaluation it was clear that bilayer tablet of Cefuroxime axetil and Potassium clavulanate can be successfully prepared.

Table 4 Evaluation tests before compression

| Formulation Code | Bulk(or Pour) Density (mg/ml) | Tapped density (mg/ml) | Hausner's ratio | Carr's index | Angle of repose. |
|------------------|-------------------------------|------------------------|-----------------|--------------|------------------|
| C1 | 0.543 | 0.608 | 1.12 | 10.69 | 23° 87' |
| F1 | 0.603 | 0.742 | 1.23 | 18.73 | 29°31' |
| F2 | 0.615 | 0.720 | 1.17 | 14.58 | 25° 82' |
| F3 | 0.592 | 0.663 | 1.12 | 10.70 | 24°12' |

Table 5 Evaluation test after compression

| Formulation Code | Thickness (mm) | Weight Variation (%) | Hardness (kg/cm ²) | Friability (%) | Disintegration Time | Drug Content (%) | |
|------------------|----------------|----------------------|--------------------------------|----------------|---------------------|-------------------|-----------------------|
| | | | | | | Cefuroxime axetil | Potassium clavulanate |
| C1F1 | 6.15 | ± 4.0 | 11.5 | 0.42 | 8 min 26 sec | 101.2 | 95.10 |
| C1F2 | 6.10 | ± 2.0 | 12.8 | 0.40 | 12 min 52 sec | 96.9 | 98.40 |
| C1F3 | 6.10 | ± 3.0 | 11.9 | 0.41 | 9 min 50 sec | 99.4 | 102.1 |

Table 6 In vitro release of cefuroxime axetil

| Time (min) | Drug Release of Cefuroxime axetil (%) | | |
|------------|---------------------------------------|-------|-------|
| | C1F1 | C1F2 | C1F2 |
| 15 | 66.1 | 71.51 | 75.95 |
| 30 | 74.1 | 83.54 | 90.89 |
| 45 | 85.21 | 92.11 | 96.74 |
| 60 | 92.1 | 95.61 | 97.1 |

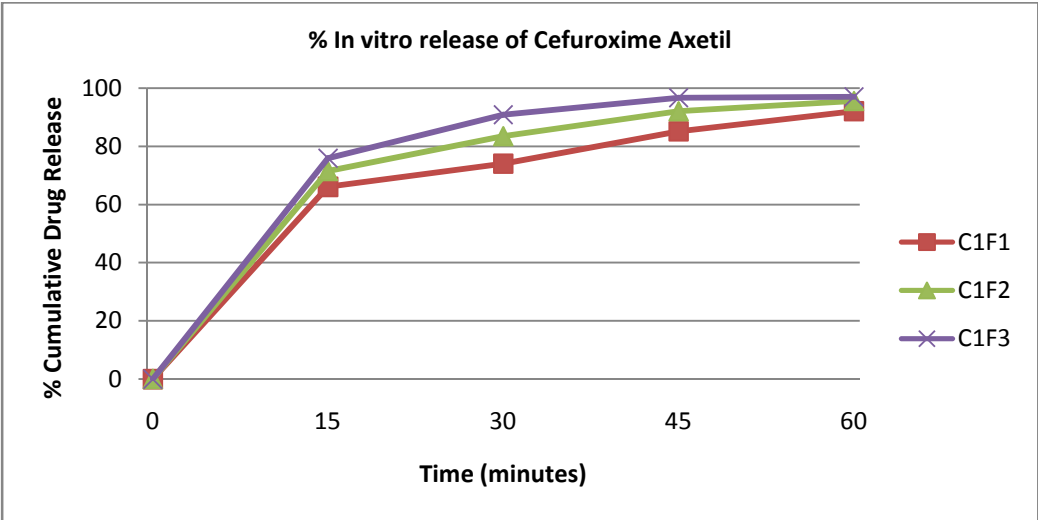


Figure 1 In vitro release of Cefuroxime axetil

Table 7 In vitro release of Potassium clavulanate

| Time (hr) | Drug Potassium clavulanate (%) | | |
|-----------|--------------------------------|-------|-------|
| | C1F1 | C1F2 | C1F3 |
| 1 | 76.42 | 79.16 | 85.1 |
| 2 | 80.94 | 87.1 | 93.51 |
| 3 | 84.61 | 89.41 | 94.15 |
| 4 | 91.05 | 94.2 | 96.98 |
| 5 | 92.1 | 95.92 | 97.25 |

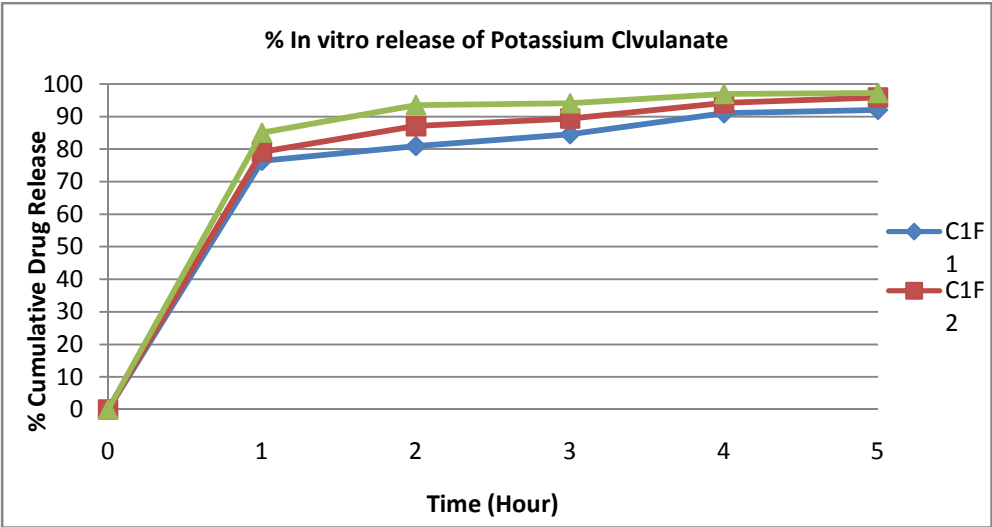


Figure 2 In vitro release of Potassium clavulanate

CONCLUSION:

The present research work was carried out to develop a bilayer tablet of Cefuroxime axetil as immediate release layer by using superdisintegrant Crosscarmellose and Potassium clavulanate as sustained release layer by using HPMC K4M. The results of current study clearly shows that bilayer tablet was developed as a stable dosage form and promising potential of Cefuroxime axetil and Potassium clavulanate bilayer tablet as an alternative to the conventional dosage form.

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