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Research Article

CAPSULE IN CAPSULE DOSAGE FORM WITH MINI TABLETS FOR THE TREATMENT OF HELICOBACTER *PYLORI*

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ABSTRACT

The current investigation involves proton pump inhibitor based therapy (Lansoprazole + Clarithromycin + Amoxicillin) combining three drugs with Capsule in capsule technology for the treatment of Helicobacter *pylori* improving patient convenience and compliance.
For delivery of Amoxicillin and Clarithromycin in stomach, combination mini tablets were formulated by direct compression method of the two drugs. Evaluation of the blend flow properties were carried out on powder blends and subsequently compressed to formulate mini tablets and evaluated for physicochemical properties, drug content and in vitro release study. The optimized formulation was subjected to short term stability study at accelerated conditions of temperature and relative humidity of 40ºC ± 2ºC and 75% ± 5% RH and evaluated at required time intervals for physical appearance and drug content. All evaluation results were found to be within the acceptable range. Lansoprazole being acid labile was filled in size 5 capsules and capsules were enteric coated with Eudragit S 100 for intestinal delivery. For final delivery of combination doses, the mini tablets were filled into the 00 size capsules and an enteric coated Lansoprazole capsule was placed in it implementing capsule in capsule technology. These capsules were evaluated as the final dosage forms for the drug content and in vitro release profile. All the tests exhibited results within an acceptable range. Hence capsule in capsule dosage form can be a good alternative for the delivery of three drugs for the treatment of H.*pylori* infection for better patient compliance.

KEYWORDS: Mini tablets, capsule in capsule, Lansoprazole, Clarithromycin and Amoxicillin, Eudragit S 100.

INTRODUCTION

Helicobacter *pylori* (H. *pylori*) is the microorganism responsible for the most frequent and persistent bacterial infection worldwide. H. *pylori* is a gram negative, spiral shaped bacterium that attach to or just above gastric mucosa. These remain persistent in the stomach and may not cause clinical illness for many years after infection. H. *pylori* infection is chronic and if acquired remains life long, unless eradicated by antibiotics.[1-3]

Mechanism of H.*pylori*

The H. *pylori* bacteria enter into the stomach and attach to the lining of the stomach and produce poisonous substances which increase the secretion of water and electrolytes in the stomach and cause cell death of the stomach lining. This causes tissue damage and results in ulcers of stomach lining.[3 ,4]

There are different therapies for treating H. Pylori. The standard triple therapy is a proton pump inhibitor (PPI) and 2 or 3 antibiotics, levofloxacin containing triple therapy, Bismuth-containing quadruple therapy, sequential therapy and Concomitant therapy.[5,6]

The first line treatment is the PPI based triple therapy (Lansoprazole + Clarithromycin + Amoxicillin) which is approved by the US-FDA.[7]

The current therapy includes different dosage forms in high doses, which may cause inconvenience to the patient and can cause dose dumping and toxicity. There is no combination dosage form available for the same, which can help in patient compliance and convenience to patient.[3, 8-10]

MINI TABLET DOSAGE FORM

Mini-tablets consist of round, cylindrical tablets — typically 2 to 3 mm in diameter — that are produced by direct compression. Mini-tablets offer finished dosage form flexibility in that they can be delivered as capsules, sachets or compressed into larger tablets that after disintegration, release these subunits as multiple dosage forms. Mini tablets are good substitutes for granules and pellets because they can be manufactured relatively easily. Mini-tablets are finding increasing use as paediatric and geriatric dosage forms, since they are easier to swallow than conventional tablets and capsules. In addition, they can be used to meet a full range of dissolution profiles, including delayed-release, controlled-release and combination-release profiles.[11-13]

CAPSULE IN CAPSULE TECHNOLOGY

Capsules are solid dosage forms in which the medication contained within gelatine shells. Recent Advancements in Capsule System are Duocaps which involves inserting a smaller pre-filled capsule into a larger liquid-filled capsule. The inner capsule of this delivery system can contain liquid, semi-solid, power or pellets, while the outer capsule can either be a liquid or semi-solid formulation. This single dosage unit with such varied uses allows clients to combine incompatible APIs, deliver compounds to two different regions if the GI tract, and the ability to add enteric coating in order to meet targeted release profiles. [14-16]. Thus the aim of the present work was to formulate a

combination dosage form to improve patient convenience and compliance.[3]

MATERIALS AND METHODS

Materials

Clarithromycin and Amoxicillin was a generous gift from Unichem laboratories (Goa-India), Lansoprazole was gifted by Mylan laboratories (Hyderabad-India), Eudragit S 100 and PEG 400 were purchased from Evonik Industries Mumbai-India and S.D Fine chemicals, Mumbai respectively.

METHODS

Enteric Coated Lansoprazole Capsules

Formulation of Enteric Coated Lansoprazole Capsules

30 mg of Lansoprazole was weighed and filled in size 5 capsules. Various enteric coating solutions were formulated and an optimized formula was selected for coating. The filled capsules were coated using dip coating technique and air dried for 12 h. The coated capsules were placed in 00 size capsules containing the drug formulation and used for further characterization. The formula is given in Table 1.

Evaluation of Lansoprazole Capsules

Assay

Enteric coated capsule containing drug equivalent to 30 mg was analysed spectrophotometrically by diluting suitably with methanol. The value obtained was used to calculate % drug content.

Weight Variation

The gain in weight of capsules containing drug after coating was found out.

In-vitro Drug Release

In-vitro release of Lansoprazole from the enteric coated capsules was carried out in phosphate buffer pH 6.8 and samples were withdrawn at intervals of 1h upto 4h. Samples were analysed spectrophotometrically at 283.8 nm with suitable dilution and the % drug release was calculated.

COMBINATION MINI TABLET DOSAGE FORM

Preparation of Mini Tablet Blends

Accurately weighed quantities of drugs and excipients were passed through sieve no. 20 and 40. Drug and excipients (excluding lubricant) were added in geometric proportions in a polybag and mixed thoroughly for 10 min. The lubricants were finally added to blends to get lubricated blends of Amoxicillin and Clarithromycin. The flow properties of the blends were evaluated. The formula is given in table 2.

EVALUATION OF BLEND FLOW PROPERTIES

Angle of repose

The angle of repose was determined by the fixed funnel method. A funnel was fixed at a height of 2 cm above a flat horizontal surface. The powder was allowed to flow through the funnel and the height 'h' of the pile and radius 'r', of the base was noted. Angle of repose was determined by following equation

$$\tan ø = h/r$$

where h = height of pile, Ø = angle of repose,
r = radius of base pile

Bulk Density And Tapped Density

The blends were introduced in a 100 ml measuring cylinder and initial volume was noted as bulk density. After the initial volume was observed, the cylinder was allowed to tap its own weight from a height of 2.5 cm. This was done using a tapped density apparatus (Campbell Electronics). The tapped density was measured after 100 taps until no further change in volume was noted.

Bulk density and tapped density were determined by the following formulae,

Bulk density (BD) = Weight of blend / Initial volume
Tapped Density (TD) = Weight of blend / Tapped volume

Compressibility Index (Carr's Index)

$$\text{Compressibility index} = \rho\text{tapped}-\rho\text{bulk} / \rho\text{tapped} \times 100$$

Hausner's ratio

Hausner's ratio was determined by the equation

$$\text{Hausner's ratio} = \rho \text{ tapped} / \rho \text{ bulk}$$

Formulation of Amoxicillin Trihydrate and Clarithromycin Mini Tablets

Amoxicillin and Clarithromycin mini tablets were formulated using direct compression method by using a 10 mm punch (M/s. Karnavati Engineering Limited, Mumbai) according to formula given in table 2. 4 mini tablets containing the required equivalent dose were filled in 00 size capsules for further characterization.

CHARACTERIZATION OF MINI TABLETS

Uniformity of weight

The uniformity of weight was carried out by weighing 20 randomly selected mini tablets from each batch. The average weight was calculated and compared with the individual mini-tablet weights.

Thickness

Ten tablets were randomly selected from each batch and the thickness of each individual tablet was measured using a digital Vernier calliper (Yamayo Bliss Classic).

Hardness

Six tablets were randomly selected from each formulation and the hardness of each tablet was determined using Monsanto hardness tester (Pathak electrical works (PEW), Mumbai). It was expressed in $Kg/cm^{2.}$

Drug Content

The mini tablets were powdered. Drug content of amoxicillin was analysed by UV spectrophotometer (Shimadzu UV 1800, Japan) at 229.20 nm using methanol. Clarithromycin was analysed using 0.1 N HCl., FC reagent (1: 2) and 20% sodium carbonate at 761.50 nm using UV spectrophotometer against 0.1 N HCl as blank. The values obtained were used to calculate the concentration of drugs.[17]

In-Vitro Release Study

The In-Vitro release study was carried out in dissolution apparatus USP type I (DBK Instruments, Mumbai). 4 mini tablets containing equivalent dose of the drug was added into 00 size capsules and placed in the basket of the dissolution apparatus containing 0.1N HCl pH1.2. The temperature was maintained at 37 ± 0.5ºC. Samples were analysed spectrophotometrically at 229.20 nm and 761.5 nm with suitable dilutions and percentage drug release was calculated. Graphs of percentage drug release versus time were plotted.

Stability Studies

Short term stability study was performed on optimized formulation. The optimized formulation was subjected to short term stability at accelerated conditions of temperature and relative humidity of 40ºC ± 2ºC and 75% ± 5% RH for a period of 3 months. Samples were withdrawn at the interval of 1 month, 2 months and 3 months and evaluated for physical appearance and drug content.

CAPSULE IN CAPSULE WITH MINI TABLET FORMULATION

Formulation

4 tablets containing dose equivalent to 250 mg and 125 mg of Amoxicillin and Clarithromycin respectively were filled in 00 size capsules. An enteric coated size 5 capsule containing Lansoprazole 30 mg was placed in this larger capsule containing the tablets. The capsule was sealed using hydro-alcoholic solution of ethanol: water (1:2).

EVALUATION

Drug Content

00 size capsule containing mini tablets and size 5 enteric coated Lansoprazole capsule was taken. The tablets were powdered and drug content for amoxicillin was analysed by UV spectrophotometer at 229.20 nm using methanol. Clarithromycin was analysed using 0.1 N HCl., FC reagent (1: 2) and 20% sodium carbonate at 761.50 nm using UV spectrophotometer against 0.1 N HCl as blank. The values obtained were used to calculate the concentration of drugs. Enteric coated capsule containing drug equivalent to 30 mg was analysed spectrophotometrically by diluting suitably with methanol. The value obtained was used to calculate % drug content.

In-Vitro Release Study

The In-Vitro release study was carried out in dissolution apparatus USP type I.

00 size capsules containing mini tablets and size 5 enteric coated Lansoprazole capsule was placed in the basket of the dissolution apparatus containing 0.1N HCl pH1.2. The temperature was maintained at 37 ± 0.5ºC. Samples were analysed spectrophotometrically at 229.20 nm and 761.5 nm with suitable dilutions. The medium in the dissolution apparatus was changed to phosphate buffer pH 6.8 and samples were withdrawn at intervals of 3, 4, 5 and 6 h. Samples were analysed spectrophotometrically at 283.8 nm with suitable dilution and the % drug release was calculated. Graphs of percentage drug release versus time were plotted.

RESULTS AND DISCUSSION

Enteric Coated Lansoprazole Capsules

Formulation of Enteric Coated Lansoprazole Capsules

30 mg of Lansoprazole was weighed and filled in size 5 capsules. The cap and the body were locked and sealed using hydro-alcoholic solution of ethanol and water (1:2 ratio) and air dried. Enteric coating solutions C1, C2 and C3 were prepared as per formula in table 1. C2 and C3 caused the capsule to remain sticky, thus C1 was selected as optimized formula for enteric coating of the capsules.

EVALUATION OF LANSOPRAZOLE CAPSULES

Assay

Drug content was analysed and was found to be 28.89 mg. The percent drug release was 96.3%.

Weight Variation

The change in weight of capsules before and after coating was noted. It was found that there was about $\leq$ 10 mg weight gain after coating of capsules.

In-Vitro Drug Release

The enteric-coated Lansoprazole capsule showed a gradual release upto 98.52% for 4 h. Thus, it was concluded that Lansoprazole showed sufficient release at the intestinal pH. Graph shown in Figure 1.

COMBINATION MINI TABLET DOSAGE FORM

Preparation Of Mini Tablet Blends

The tablet blend was prepared by procedure stated in 3.2.

EVALUATION OF BLEND FLOW PROPERTIES

The blends of different formulations were evaluated for angle of repose, bulk and tapped density, Carr's compressibility index and Hausner's ratio. The bulk density of blends was found to be between 0.5 and 0.58 g/cm³. This indicates good packing capability. Hausner's ratio ranged from1.11 to 1.18, which indicates good flowability. Carr's index was found to be between 8.4 and 15, showing fair to passable flow characteristics. The angle of repose of all the formulations was within the range 32º to 35ºS. This indicates that the blends had passable flow properties from the literature reviewed.[18] Results shown in table 3.

FORMULATION OF AMOXICILLIN TRIHYDRATE AND CLARITHROMYCIN MINI TABLETS

Amoxicillin and Clarithromycin mini tablets were formulated using direct compression method according to formula given in

table 2. The prepared blends of amoxicillin and Clarithromycin tablets were compressed using BB tooling of 10 mm punches of 12 station rotary tablet compression machine.

CHARACTERIZATION OF MINI TABLETS

Weight Variation

The weights of the tablet were found in the range of 148.75 mg to 152.5 mg which complies with the standard limits according to the referred literature.[19]

Thickness

The thickness of the tablets ranged from 2.65 to 2.70 which is within the limit (± 5 % of a standard value.)[18]

Hardness

The hardness ranged from 4-5 kg/cm^2 which compiled with the specified standards.
Results are shown in table 3.

Drug Content

Since, formulations T1, T2, and T3 showed highest percentage of drug content compared to T4, T5 and T6; they were selected as the optimised formulations for further evaluation. Graph shown in figure 2.

In-Vitro Release Study

From the comparative release studies of formulation T1, T2, and T3 as shown in the figure 3, it was concluded that formulation T2 showed maximum in-vitro release of 95.104 % and 90.756 % for Amoxicillin and Clarithromycin respectively, compared to T1 which showed release of 93.258 % and 87.127 % for Amoxicillin and Clarithromycin respectively and T3 showed release of 94.269 % and 83.49 % for Amoxicillin and Clarithromycin respectively. Thus, T2 was selected as the optimized tablet formulation. Graph shown in Figure 3.

Stability Studies

For stability evaluation, at the end of the 1 month, 2 months and 3 months one capsule containing the optimized tablet formulation T1 was tested for drug content. Results showed that there were no significant changes in its spectral properties or any visible changes.

CAPSULE IN CAPSULE WITH MINI TABLET FORMULATION

Formulation

4 tablets containing dose equivalent to 250 mg and 125 mg of Amoxicillin and Clarithromycin respectively were filled in 00 size capsules. An enteric coated size 5 capsule containing Lansoprazole 30 mg was placed in this larger capsule containing the tablets. The capsule was sealed using hydro-alcoholic solution of ethanol: water (1:2) and evaluated for drug content and in-vitro drug release.

Evaluation

Drug Content

The % drug content for Amoxicillin was found to be 96.6%, for Clarithromycin the drug content was found to be 94.93% and Lansoprazole it was found to be 93.87%. All the values were in pharmacopoeial acceptance limit; hence the formulation was carried forward for in-vitro release.

***In-Vitro* Release Study**

In the mini tablets, Amoxicillin showed release upto 93.93% while Clarithromycin showed release upto 90.756% at the end of 2 h. The enteric-coated Lansoprazole capsule showed a gradual release upto 98.52% for 4 h in phosphate buffer pH 6.8.

As the drug release in combination dosage form was at required site in acceptable amount, it was concluded that capsule in capsule technology worked efficiently for combining the three drugs for improved patient compliance.

DISCUSSION

FDA approved medication for treatment of H.*pylori* includes Amoxicillin, Lansoprazole Clarithromycin taken individually which may be inconvenient for patient to take.

An attempt was made to prepare combination dosage form (Amoxicillin + Clarithromycin + Lansoprazole) for the treatment of H.pylori infection. The approach selected was capsule in capsule with inner enteric coated capsule of Lansoprazole and outer capsule was of mini tablets of amoxicillin and Clarithromycin. Several evaluative tests were carried out on all the formulations as well as final capsule in capsule formulation. The APIs were characterised for identity and purity by FTIR spectroscopy and for blend flow properties by calculation of angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio. Subsequently the blends was compressed into mini tablets and were further evaluated for hardness, disintegration, thickness, drug content and in-vitro release studies. From evaluation studies T2 formulation of mini tablets was considered as the optimized formulation. Thus capsule in capsule dosage form which is used for combining the 3 drugs improves the patient convenience and compliance.

TABLE 1: FORMULATION OF ENTERIC COATED LANSOPRAZOLE CAPSULES

Ingredients	C1 (g)	C2 (g)	C3 (g)
Eudragit S 100	8 g	12 g	15 g
Methylene chloride	21 g	16.8 g	13.5 g
Ethanol	70 g	70 g	70 g
PEG 400	0.8 g	1.2 g	1.5 g

TABLE 2: FORMULATION OF AMOXICILLIN TRIHYDRATE AND CLARITHROMYCIN MINI TABLETS

Ingredients	T1 (mg)	T2 (mg)	T3 (mg)	T4 (mg)	T5 (mg)	T6 (mg)
Amoxicillin Trihydrate	250	250	250	250	250	250
Clarithromycin	125	125	125	125	125	125
Microcrystalline cellulose	77	77	77	115.5	115.5	115.5
HPMC E5	11.55	15.4	19.25	11.55	15.4	19.25
Sodium Starch Glycolate	7	7	7	7	7	7
Talc	1	1	1	1	1	1
Sodium Starch Glycolate	2	2	2	2	2	2

TABLE 3: RESULTS OF POWDER FLOW PROPERTIES AND RESULTS OF UNIFORMITY OF WEIGHT THICKNESS AND HARDNESS OF MINI TABLETS

Formulation code	Bulk density	Tapped density	Hausner's ratio	Carr's index	Angle of repose	Weight Variation (±7.5%) mg	Average Thickness (mm)	Hardness (kg/cm^2)
T1	0.54	0.6	1.11	10	32	150	2.68	4 - 5
T2	0.56	0.65	1.160714	13.84615	33	150.5	2.65	4 - 5
T3	0.58	0.65	1.12069	10.76923	34	148.75	2.67	4 - 5
T4	0.55	0.65	1.181818	15.38462	35	152.5	2.68	4 - 5
T5	0.54	0.59	1.092593	8.474576	35	150.5	2.70	4 - 5
T6	0.5	0.59	1.18	15.25424	32	149	2.69	5- 5

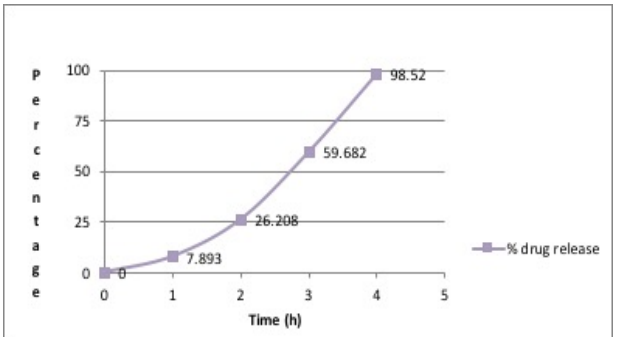


FIGURE 1: Results of in vitro drug release study from an enteric coated Lansoprazole capsule in phosphate buffer pH 6.8.

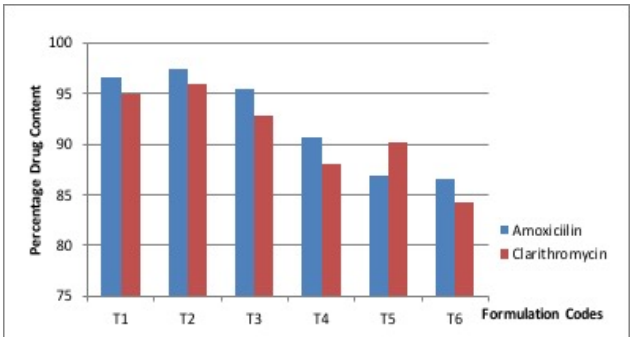
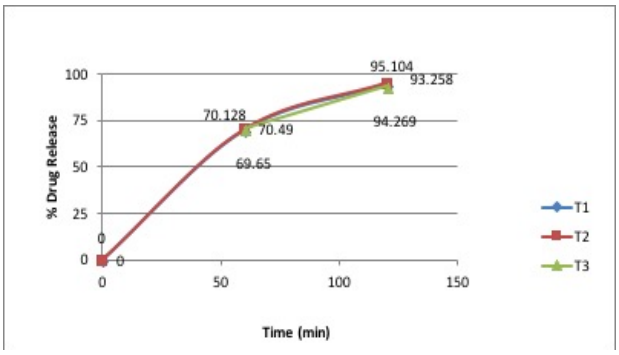


FIGURE 2: Comparison of percentage drug content in different mini tablet formulations formulated (T1 – T6).



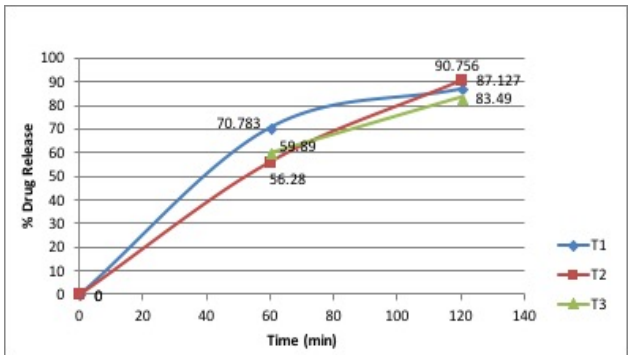


Figure 3: Comparison of drug release profiles for Amoxicillin and Clarithromycin from Different min tablet formulations T1, T2 and T3 in 0.1 N HCl pH 1.2

CONCLUSION

From the results of the research, it was concluded that the proposed aim of combination dosage form for the treatment of H.pylori and helping in patient convenience by formulation of novel dosage forms were achieved successfully.

The future scope of study is to carry was solubility enhancement technique on the drugs and to find out the actual reduction in dose by conducting in vivo studies. The effectiveness of combination dosage form can also be evaluated in vivo as future objective of this research.

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