ORIGINAL ARTICLE

Formulation Development and Evaluation of Tablet in Tablet Dosage form to Proffer a Quick and Protracted Relief in Gastritis and Allied Gastric Disorders

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Abstract

Purpose: The contemporary investigation was intended to extend and appraise uniqueness of the tablet in tablet formulation with a perception to proffer a quick and protracted relief in gastritis and allied gastric disorders. **Materials and Methods:** The possible drug-excipient interaction between Esomeprazole Magnesium and formulation constituents/excipients of core and outer tablet was envisaged to map the batch composition formulas for the core tablets. The core tablets were compressed using 6.5 mm die punch (concave) set and outer tablets (devoiding core tablet) were compressed using 14 mm die punch (concave) set with optimized compression load and speed. Based on performance outcome of core tablet and outer tablet batches, during the assessment of the post compression parameters, three batches for tablet in tablet were purposed and compacted, which were later subjected to *in vitro* release kinetics. The short-term accelerated stability testing of the varied batches of tablet in tablet formulations was executed to predict the environmental influence over the quality of finalized formulation and to ensure that no alteration has been brought in to the formulation during the course of manufacturing process that could negatively impact its stability. The optimized tablet in tablet formulation was compared with the commercially accessible enteric coated Esomeprazole tablet. The maximum plasma concentration (C_{max}, µg/mL) and the corresponding time (T_{max}, hour) for the two treatments in each rabbit were estimated through high-performance liquid chromatography in the plasma concentration data. **Results:** The post-compression parameters of the core tablets revealed that the CT-26 batch, comprising polyethylene glycol as binder and sodium starch glycolate as disintegrant, was best among rest, of all the batches (CT-1 to CT-27), with crushing strength of 3.57 ± 0.115 kg/cm^2, Friability 0.188 ± 0.002 (% loss), disintegration time of 52.66 ± 0.57 s, and % drug content was found to be 100.31 ± 0.32. The post-compression parameters of outer tablet, reveals that the OT-2 batch, comprising microcrystalline cellulose as disintegrant, was best among rest, out of all batches (OT-1 to OT-9), with crushing strength of 5.55 ± 0.132 kg/cm^2, Friability 0.098 ± 0.004 (% loss), and disintegration time of 161.33 ± 0.57 s. The analysis of the entire tablet in tablet (T in T-1 to T in T-3) batches reveals that of the T in T -3 (comprising of CT-26 and OT-2) was the best batch, among rest of all batches (T in T-1 to T in T-3), with mean weight 776.95 ± 0.394 mg, thickness 6.516 ± 0.028 mm, crushing strength of 6.10 ± 0.276 kg/cm^2, Friability 0.193 ± 0.006 (% loss), disintegration time of 189.33 ± 0.577 s, and % drug content 97.36 ± 0.07. The *in vitro* release of Esomeprazole magnesium from varied tablet in tablet formulations were also assessed by integrating drug release statistics into diverse release pharmacokinetics models. The maximized regression values (0.991) for tablet in tablet formulations demonstrated the sensible linearity through Higuchi pharmacokinetic model, signifying the formulations as modified release formulation. The accelerated stability studies have demonstrated the consistent sunset yellow color of the optimized formulation, with smooth surface exclusive of any flaws or cracks. The disintegration time of 195.21 ± 1.468 s, and % drug content was found to be 96.79 ± 0.539. The observed mean C_{max} for optimized formulation, T in T-3 (0.68 ± 0.98 mg/mL) was higher than that obtained from the enteric coated commercial formulation (0.56 ± 0.37 mg/mL). The mean residence time was 3.78 h and the area under the curve was 2.912 ± 1.53 µg/mL/h. From the *in vitro* dissolution studies, it was found that the maximum drug release was achieved in about 60 min. Hence, from the *in vitro* and *in vivo* results, it

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was evident that the release of esomeprazole from the optimized (T in T-3) formulation was quicker than the conventional commercial formulation with relative bioavailability (F_R %) 91.861%. **Conclusion:** In the present study, the tablet in tablet technology was used to formulate an immediate release formulation, in which Esomeprazole Magnesium; an acid labile drug was kept in core tablet and the outer tablet confining acid neutralizing agents. The constituents of core tablet and outer tablet release simultaneously in the stomach acidic environment. The outer tablet containing acid neutralizing agents counterbalance the gastric environment and thus providing favorable pH environment for the release of esomeprazole in stomach. Both the constituents act in synergy to produce desired pharmacological action. This will provide instantaneous relief with the release of acid neutralizing agents from the outer tablet and proffer prolong relief (with the release of esomeprazole from the core table) from the gastric symptoms due to irreversible binding to cysteine residues of the H^+/K^+ATPase. The clinical action of each drug component will not alter and exhibited their action in synergy. This will offer better therapeutic efficacy and improve patient compliance.

Key words: Accelerated stability studies, compression coating, esomeprazole magnesium, modified release, Proton pump inhibitors

INTRODUCTION

The proton pump inhibitors (PPIs) are frequently recommended to treat, diverse hypergastrinemic complications due to their superior acid suppression, safety, and patient acceptance. All PPI's are acid-labile weak bases hence enteric coated to retard drug degradation in stomach.[1] All PPI's are typically formulated additionally with sodium bicarbonate to provide momentary elevation in pH, and to prevent drug degradation at the lower pH environment. Furthermore, sodium bicarbonate encourages the release of gastrin that in turns activates the H+/K +ATPase pump, permitting swift inhibition of acid production.[2] They are principally prodrugs which get triggered to active sulfenic acid and sulfonamide moiety after accumulating in canaliculi of stimulated parietal cell. Here they bind irreversibly and covalently to cysteine residues on the alpha subunit of the H+/K +ATPase through disulfide linkage and restrain acid production, up to 36 h.[3] All PPI are extensively metabolized in liver through cytochrome P450 isozyme CYP2C19 and CYP3A4.[4,5]

Esomeprazole is the S (levo) - enantiomer of racemic Omeprazole.[6] Its highly protein bound drug with plasma protein binding up to 97%.[7] In contrast to racemic Omeprazole and other PPI, Esomeprazole has superior pharmacokinetic profile, in reference to isozyme CYP2C19. It has sluggish hepatic clearance which consequences in higher systemic exposure and bioavailability that invariably tenders superior efficacy in management of acid peptic disorders.[8] The biotransformation of Esomeprazole magnesium is ensued by hepatic enzymes cytochrome P450 involving two different isoforms CYP2C19 and CYP3A4.[9]

Tablet in tablet is an Innovative and Pragmatic approach, where a tablet is compressed with a core tablet in the center.[10] In other words, the core tablet is completely enclosed in the outer tablet. It is also expressed as compression coated tablet where outer tablet plays the role of coating over the core tablet.[11] Drug degradation at the lower pH in stomach can be prevented by placing such acid labile drug in core tablet.[12] Certain drugs like non-steroidal anti-inflammatory drugs that are known to cause gastric irritation, such drug induced complications can be evaded by placing such drug components in core tablet thus outer tablet will act as barrier evading direct interaction of irritant drug with the stomach.[12] The Formulations prepared in the form of tablet in tablet, are more stable at varied environmental conditions, in contrast to coated tablet formulation prepared through traditional coating techniques.[13] The present research was an attempt to develop a unique modified immediate release formulation in which both API's (in core and in outer tablet) work in synergy and produce meaningful pharmacological outcome in gastritis and allied gastric disorders besides improving patient compliance.

MATERIALS AND METHODS

Materials

The Esomeprazole Magnesium (IP) was acquired as a gift sample from Sun Pharmaceutical Industries Ltd., Paonta Sahib, Himachal Pradesh, India, and all other constituents or excipients, either analytical grade or laboratory grade, were procured from the local vendor.

Methods

Determination of acid neutralization capabilities of key constituents of outer tablet

To evaluate the acid neutralization capabilities, batches F-1 to F-11 [Table 1] were purposed with varied composition of constituents with documented competence of acid neutralization. The composition of various batches was mapped and explored for their acid neutralization capabilities. The acid neutralization capability was measured by the Rossett-Rice test through the process of back titration. This involves dissolving the outer tablet formulation constituents (possessing acid neutralizing capabilities) in an excess of hydrochloric acid and titrating this acidic solution against a known concentration of base until the endpoint is achieved. The molarity of Hydrochloric acid neutralized is equivalent to the variation between the moles of

HCl incorporated to total number of moles required for the back titration by the base (NaOH).[14]

Moles of acid neutralized = Moles of HCl added-Moles of NaoH Required

$$= (\text{Vol}_{HCl} \times \text{Molarity}_{HCl}) - (\text{Vol}_{NaoH} \times \text{Molarity}_{NaoH})$$

Acid neutralization/g of formulation constituents = Moles of acid neutralized/g of formulation constituents.

Batch composition of outer tablet, for compression, and analysis

The batch composition formulas for outer tablet (OT-1 to OT-9) were prepared from the batch with best acid neutralizing capabilities determined earlier [Table 2]. Furthermore, the varied batches were distinguished with the aid of color comprising particular disintegrant. The batches containing microcrystalline cellulose as a disintegrant (OT-1 to OT-3) were supplemented with sunset yellow dye in starch paste (binder) to distinguish it from rest of batches containing dissimilar disintegrant. Likewise, the batches formulated with HPMC as a disintegrant (OT-7 to OT-9) were additionally aided with tatrazine dye and the batches comprising of sodium starch glycolate as a disintegrant (OT-4 to OT-6) were devoid of any coloring dye in the binding paste, rendering it white color tablets.

Drug-excipient Interaction studies

Possible drug-excipient interaction between Esomeprazole Magnesium and formulation constituents/excipients of core and outer tablet was envisaged through FTIR Spectrophotometric technique [Figure 1]. The FTIR spectroscopy can sense vibrational changes, which could be the precursor of possible intermolecular interactions between drug and formulation components.[15] To execute compatibility studies of Esomeprazole Magnesium and formulation constituents, they were mixed in ratio of 1:1 and these observational blends were kept at 40°C ± 2°C/75% ± 5% RH, in stability chamber for 4 weeks. After the end of 4th week the IR spectrum of observational blends were obtained under a scanning range between 4000 cm^{-1} and 400 cm^{-1} and compared with standard spectrum for appearance of new peaks/disappearance of absorption peaks or for reduction in peak intensity.[16] All IR spectrums were interpreted for the identification of compounds.

Preparation of granular blend and compression of core tablet

The batch composition formulas (CT-1 to CT-27) for core tablet were prepared based on drug-excipients compatible studies [Table 3]. They were further distinguished with the aid of color comprising of particular binder in the

Table 1: Composition and acid neutralization capabilities of different batches (F-1 to F-11)

Ingredients (mg)	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9	F-10	F-11
Aluminum hydroxide	250 mg	200 mg	150 mg	100 mg	300 mg	300 mg	300 mg	300 mg	250 mg	250 mg	250 mg
Magnesium hydroxide	250 mg	200 mg	150 mg	100 mg	250 mg	200 mg	150 mg	100 mg	200 mg	150 mg	100 mg
Magnesium aluminum silicate	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg
m.mol H+/g of acid neutralizing formulation	6.898	7.968	6.896	5.892	7.531	7.37	6.861	5.317	8.107	7.854	6.327

Table 2: Batch composition of outer tablet, for compression, and analysis (OT-1 to OT-9)

Ingredients (mg)	OT-1	OT-2	OT-3	OT-4	OT-5	OT-6	OT-7	OT-8	OT-9
Aluminum hydroxide	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg	250 mg
Magnesium hydroxide	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg
Magnesium aluminum silicate	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg
Dimethyl polysiloxane	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg
Starch paste (corn starch)	40 mg	40 mg	40 mg	40 mg	40 mg	40 mg	40 mg	40 mg	40 mg
Microcrystalline cellulose	25 mg	50 mg	75 mg	-	-	-	-	-	-
Sod. Starch glycolate	-	-	-	25 mg	30 mg	35 mg	-	-	-
HPMC	-	-	-	-	-	-	30 mg	40 mg	50 mg
Magnesium stearate	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg
Talc	30 mg	30 mg	30 mg	30 mg	30 mg	30 mg	30 mg	30 mg	30 mg
Weight of tablet	655 mg	680 mg	705 mg	655 mg	660 mg	665 mg	660 mg	670 mg	680 mg

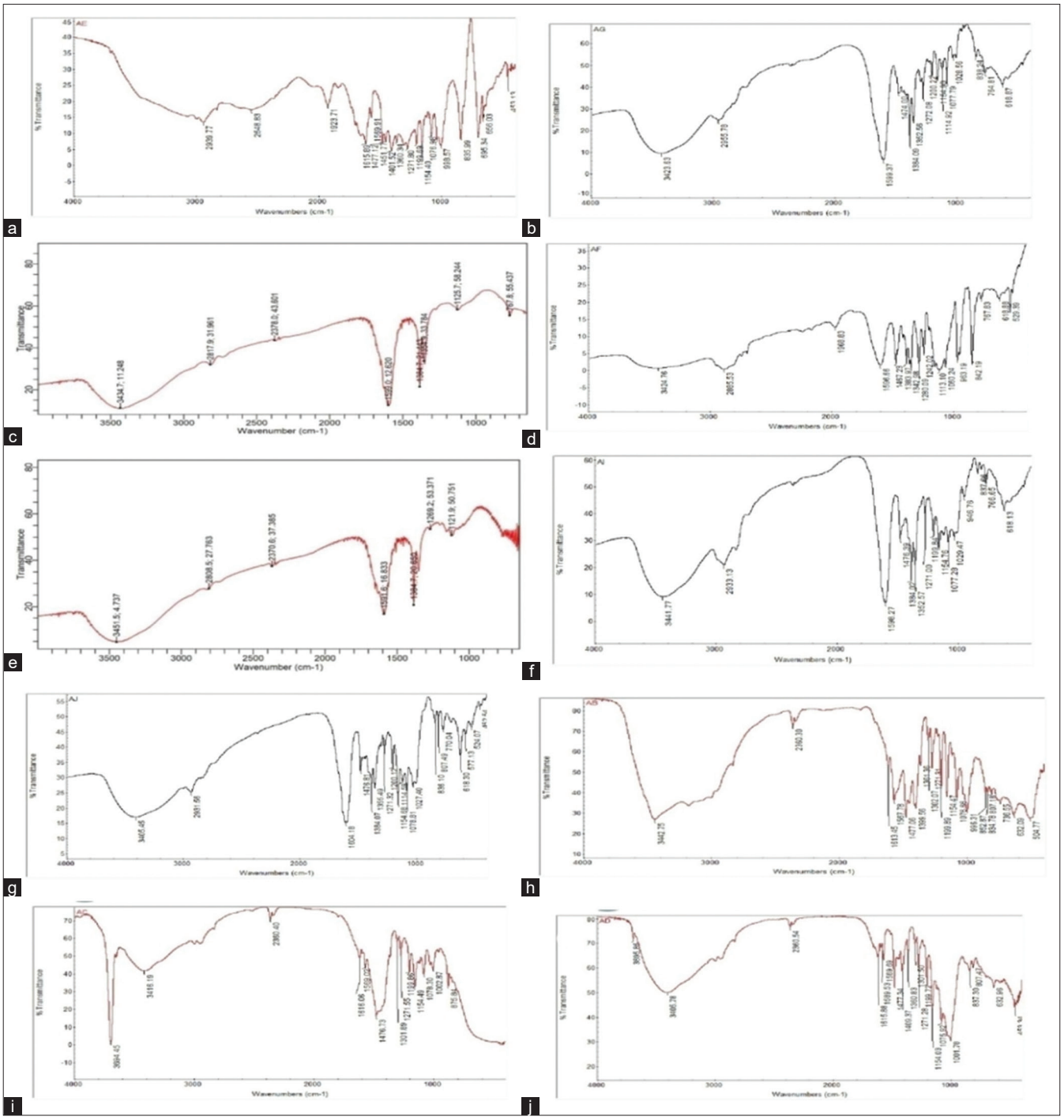

Figure 1: Fourier transform-infrared spectroscopy (FTIR) spectrums acquired after drug- excipient interaction studies: (a) FTIR spectrum of esomeprazole magnesium - sodium bicarbonate, (b) FTIR spectrum of esomeprazole magnesium with polyvinyl Pyrrollidone K-30, (c) FTIR spectrum of Esomeprazole Magnesium - Acacia, (d) FTIR spectrum of Esomeprazole Magnesium - Polyethylene glycol 4000, (e) FTIR spectrum of esomeprazole magnesium -microcrystalline cellulose, (f) FTIR spectrum of Esomeprazole Magnesium - Hydroxypropyl methylcellulose (HPMC), (g) FTIR spectrum of esomeprazole magnesium -sodium starch glycolate, (h) FTIR spectrum of esomeprazole magnesium -aluminum hydroxide, (i) FTIR spectrum of esomeprazole magnesium - magnesium hydroxide, and (j) FTIR spectrum of esomeprazole magnesium - magnesium aluminum silicate

formulation. The batches comprising polyvinyl pyrrollidone as a binder (CT-1 to CT-9) were supplemented with brilliant blue dye to distinguish it from rest of batches containing dissimilar binder. Likewise, the batches formulated with acacia as binder (CT-10 to CT-18) were additionally aided with carmosine dye and the batches comprising polyethylene glycol (CT-19 to CT-27) were supplemented with tatrazine dye.

Table 3: Batch composition of core tablet, for compression and analysis

Ingredients (mg)	CT-1	CT-2	CT-3	CT-4	CT-5	CT-6	CT-7	CT-8	CT-9
Esomeprazole	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg
Sodium bicarbonate	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg
Polyvinyl pyrrollidone K-30	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg
Acacia	-	-	-	-	-	-	-	-	-
Polyethylene Glycol 4000	-	-	-	-	-	-	-	-	-
Microcrystalline cellulose	6 mg	8mg	10 mg	-	-	-	-	-	-
HPMC	-	-	-	5 mg	6 mg	7 mg	-	-	-
Sod starch Glycolate	-	-	-	-	-	-	4 mg	5 mg	6 mg
Magnesium stearate	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg
Talc	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg
weight of tablet	93 mg	95 mg	97 mg	92 mg	93 mg	94 mg	91 mg	92 mg	93 mg
	CT-10	CT-11	CT-12	CT-13	CT-14	CT-15	CT-16	CT-17	CT-18
Esomeprazole	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg
Sodium bicarbonate	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg
Polyvinyl pyrrollidone K-30	-	-	-	-	-	-	-	-	-
Acacia	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg
Polyethylene Glycol 4000	-	-	-	-	-	-	-	-	-
Microcrystalline cellulose	6 mg	8mg	10 mg	-	-	-	-	-	-
HPMC	-	-	-	5 mg	6 mg	7 mg	-	-	-
Sod starch Glycolate	-	-	-	-	-	-	4 mg	5 mg	6 mg
Magnesium stearate	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg
Talc	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg
Weight of tablet	93 mg	95 mg	97 mg	92 mg	93 mg	94 mg	91 mg	92 mg	93 mg
	CT-19	CT-20	CT-21	CT-22	CT-23	CT-24	CT-25	CT-26	CT-27
Esomeprazole	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg
Sodium bicarbonate	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg
Polyvinyl pyrrollidone K-30	-	-	-	-	-	-	-	-	-
Acacia	-	-	-	-	-	-	-	-	-
Polyethylene Glycol 4000	15 mg	15 mg	15 mg	15 mg	15 mg	15 mg	15 mg	15 mg	15 mg
Microcrystalline cellulose	6 mg	8 mg	10 mg	-	-	-	-	-	-
HPMC	-	-	-	5 mg	6 mg	7mg	-	-	-
Sod starch glycolate	-	-	-	-	-	-	4mg	5 mg	6 mg
Magnesium stearate	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg
Talc	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg
Weight of tablet	98 mg	100 mg	102 mg	97 mg	98 mg	99 mg	91 mg	97 mg	98 mg

Evaluation of pre-compression parameters of core and outer tablets

Micromeritic properties of granular blend of core tablet

The batches of outer tablet (CT-1 to CT-9) containing polyvinyl pyrrollidone as binder was prepared by wet granulation method containing isopropyl alcohol as wetting and solubilizing agent for polyvinyl pyrrollidone. The rest of the batches from CT-10 to CT-27 were prepared by the process of slugging. All the compounds (Esomeprazole magnesium, sodium bicarbonate, and dye) were initially mixed with binder and 70% disintegrant. They were initially compressed with 14 mm die-punch set and passed through sieve no 12 to get uniform sized raw granules. They were further passed through sieve no 22 to get ideal granular size for compression. The rest of the ingredients (30% disintegrant, Magnesium stearate, and talc) were properly weighed and mixed. The micromeritic properties such as Angle of repose, density (Bulked and Tapped density), Carr's compressibility index, and

Hausner's ratio of the granular blend were appraised and reported before final compression on 6.5 mm die punch (concave) set.

Micromeritic properties of granular blend of outer tablet

The batches of outer tablet (OT-1 to OT-9) were prepared by wet granulation method using hydrolyzed starch paste as binder. The raw granules were prepared by passing the coherent wet mixture from sieve no 12. These granules were kept in a tray dryer maintained at 40°C for 12 h. The coloring dye, if added, was incorporated into the binder paste (starch paste, hydrolyzed) during its preparation. The dried raw granules were passed through sieve no 22 and mixed with residual amount of ingredients in the recipe. The micromeritic properties such as Angle of repose, density (Bulked and Tapped density), Carr's compressibility index, and Hausner's ratio of the granular blend were appraised and reported before final compression.

Evaluation of post-compression parameters of core tablet and outer tablet

The core tablets were compressed using 6.5 mm die punch (concave) set and outer tablets (devoiding core tablet) were compressed using 14 mm die punch (concave) set with optimized compression load and speed. The post-compression parameters of core tablet and outer tablet, namely, mean weight, weight variation, thickness, crushing strength, friability, disintegration time, dissolution time, and % drug content were appraised for all the batches of core tablet (CT-1 to CT-27) and outer tablet (OT-1 to OT-9) as per official compendia.

Compression and evaluation of post-compression parameters of tablet in tablet

The three batches [Table 4] were primed, based on performance outcome of core tablet (CT-1 to CT-27) and outer tablet (OT-1 to OT-9) batches, during the assessment of the post compression parameters. The batches of tablet in tablet were formulated based on decreasing merit of performance. The finest batch among the core tablet was associated with the finest batch of outer tablet. Similarly, other combinations of core and outer tablets were composed and compressed

Table 4: Batch composition of tablet in tablet, for compression and analysis

Batch	Core tablet	Outer tablet
Tablet in tablet -1 (T inT-1)	CT-2	OT-8
Tablet in tablet -2 (T inT-2)	CT-14	OT-5
Tablet in tablet -3 (T inT-3)	CT-26	OT-2

[Figure 2]. All the batches of tablet in tablet were evaluated nearly on similar stipulations and parameters as used for characterizing uncoated tablet. The in-vitro drug dissolution investigations were further extended by integrating drug dissolution data to varied drug release models viz zero order, first order, Higuchi model, Korsmeyer-Peppas model, Hixson-Crowel cube root model which further signifies the followed release mechanism.[17]

Stability studies (accelerated stability studies) for the Tablet in Tablet formulations (T in T-1 to T in T-3)

The stability testing of the tablet in tablet formulations was executed to predict the environmental influence (effect of temperature/humidity) over the quality of finalized formulation and to ensure that no alteration have been brought in to the formulation during the course of manufacturing process, that could negatively impact on its stability. The tablet in tablet formulations (T in T-1 to T in T-3) were subjected to short term accelerated stability studies as per ICH guidelines and protocol. The tablet in tablet formulations (T in T-1 to T in T-3) were placed in separate airtight glass bottles and kept in stability chamber at 40°C ± 2°C/75% RH ± 5% RH, for 3 months.[18] The samples of tablet in tablet formulations (T in T-1 to T in T-3) were withdrawn at the interval of 4 weeks, that is, on 4th week, 8th week, and finally on 12th week. The withdrawn tablet in tablet formulations (T in T-1 to T in T-3) at respective pullout period were evaluated for any variation in physical appearance/weight, crushing strength, friability, disintegration, and drug content.[18]

In vivo pharmacokinetic evaluation for optimized tablet in tablet formulation[19]

The optimized tablet in tablet (T in T-3) formulation was compared with the commercially accessible enteric coated Esomeprazole tablet (Nexpro 20 mg manufactured by Torrent Pharmaceuticals Ltd.). The study was accomplished by using three groups of rabbits (weight ≈ 2.5 kg), comprising three rabbits in the each group. All rabbits in respective groups were starved overnight but only water was allowed to them, through feeding bottles. They remained fasting for an additional 4 h, post-treatment. The rabbits in the control group (Group-I) were given, only water. The commercially available enteric coated Esomeprazole tablets (Nexpro 20 mg) were introduced to the rabbits in Group II and Group III rabbits were administered with the test formulation tablet in tablet (T in T-3). The study was carried out using a single dose crossover design amid a 7-day washout interval.[19] After administering the test and commercial formulations, the blood samples (0.5 mL) were withdrawn from the marginal ear vein and placed in tubes containing heparin at the intervals of 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 10 h. The centrifugal separation at 3000 rpm for 10 min was carried out to separate the plasma, which was then stored at −20°C until analysis. The blood samples were also taken

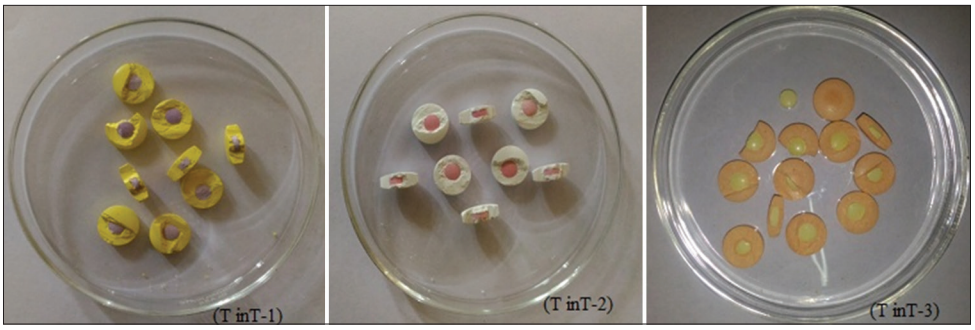

Figure 2: Tablet in Tablet (T in T-1 to T in T-3)

prior to the formulation administration, and the plasma was separated to prepare the calibration curve. The proteins were precipitated from the plasma samples using 10% perchloric acid, which was followed by 15 min of centrifugation at 4000 rpm. High-performance liquid chromatography (HPLC) was used to analyze the esomeprazole magnesium in plasma.[19] The *in vivo* experimentation was realized following CPCSEA guidelines and approved by IAEC of CT institutes of pharmaceutical sciences, Jalandhar.

HPLC methodology

The quantification of esomeprazole in rabbit plasma was done through HPLC at varied time intervals. Waters HPLC Chromatograph with UV detector and Empower software was employed to carry out the different determinations. The ODS, C-18 column (Phenomenex -250 × 4.6 mm) was used to achieve separation at ambient temperature. The blend of equal volume of buffer (6.8 g of potassium dihydrogen phosphate and 1 g of sodium hydroxide in 1 L water) and methanol was chosen as the mobile phase. The ortho phosphoric acid was engaged to adjust the pH up to 7. The mobile phase was introduced at the flow rate of 1.5 mL/min subsequent to sonication, and filtration. The samples were injected through rheodyne injector and the eluted components were detected by UV detector at 301 nm.

Determination and analysis of pharmacokinetic parameters[19]

The plasma level data from each rabbit were used to establish and analyze the pharmacokinetic parameters, which were exhibited as (±) mean standard deviation. The maximum plasma concentration (C_{max}, µg/mL) and the corresponding time (T_{max}, hour) for the two treatments in each rabbit were estimated through the plasma concentration data. For both treatments, a plot of the mean plasma concentration versus time was created. The trapezoidal rule was realized to estimate, the area under the curve from time 0 to 10 h (AUC_{0-10} µg. h/mL). The area under the tail was merged with AUC 0–10 h, to estimate the area under the curve from time 0 to 24 h (AUC_{0-24}).[19] The elimination rate constant produced by linearly regressing the elimination phase of the plasma concentration versus time curve was divided by the most recently estimated concentration to determine the area under the tail.[19] The mean residence time (MRT), a non-compartment pharmacokinetic parameter was estimated. Subsequent to the estimation of area under the first moment curve (AUC_{0-24} µg.h/mL), the relative bioavailability (F_R) of the tested formulation in comparison to the commercially available formulation was predicted through following equation:[19]

$$F_R\ (\%) = (AUC_{0\text{-}24\ h}\ (\text{Tab in Tab-3})/AUC_{0\text{-}24\ h}\ \text{commercial formulation}) \times 100$$

RESULTS

Analytical assessment of drug contenders of outer tablet in the tablet in tablet

The three model drug contenders considered for evaluation for their acid neutralization capabilities at different compositions are aluminum hydroxide, magnesium hydroxide, and magnesium aluminum silicate. The composition and discovered acid neutralization capabilities of different batches (F-1 to F-11) are demonstrated tabularly [Table 1]. During the process of evaluation for acid neutralization capabilities of varied batches, the F-9 batch was found to be the optimum composition with excellent neutralization capabilities of 8.107 mmol H^+/g of acid neutralizing formulation.

Drug-excipient interaction studies

The individual admixture of Esomeprazole Magnesium with each one of formulation component (1:1) were kept at 40°C ± 2°C/75% ± 5% RH, in stability chamber for 4 weeks, to predict the compatibility of each one of the formulation constituent/excipient with the core drug (Esomeprazole Magnesium) through FTIR Spectrophotometric technique. The spectrums obtained at the end of 4th week [Figure 1] were compared with standard spectrums and it was observed that the varied blends of Esomeprazole Magnesium with diverse formulation constituent/excipient were compatible.

Evaluation of granular blend and compression of core tablet

The micromeritic properties of the granular blend were appraised and the flow properties of the granular bland were found to be good [Table 5]. The core tablets were compressed using 6.5 mm die punch (spherical and concave shaped) set.

Evaluation of post-compression parameters of core tablet

Based on the investigation of post-compression parameters [Table 6] of the core tablets, it was observed that the CT-26 batch, comprising polyethylene glycol as binder and sodium starch glycolate as disintegrant, was best among rest of all batches (CT-1 to CT-27), with crushing strength of 3.57 ± 0.115 kg/cm^2, Friability 0.188 ± 0.002 (% loss), disintegration time of 52.66 ± 0.57 s, and % drug content was found to be 100.31 ± 0.32. The crushing strength of second finest batch, CT-14 was found to be 3.54 ± 0.155 kg/cm^2, Friability 0.283 ± 0.003 (% loss), disintegration time of 58.66 ± 1.15 s, and % drug content was found to be 100.26 ± 0.33. The crushing strength of third finest batch, CT-2 was found to be 3.45 ± 0.162 kg/cm^2, Friability 0.335 ± 0.008 (% loss), disintegration time of 69.33 ± 0.57 s, and % drug content was found to be 99.66 ± 0.90. The second finest batch (CT-14) among all, consisting of Acacia as binder and HPMC as disintegrant and third finest batch (CT-2) consisting of polyvinyl pyrrollidone as binder, and microcrystalline cellulose as disintegrant, were additionally investigated in progressive development of formulation, tablet in tablet.

Preparation of granular blend and compression of outer tablet (devoiding core tablets)

The batch composition formula (Formulation Code OT-1 to OT-9) for outer tablet was prepared on the bases of realization

Table 5: Micromeritic properties of granular blend of core tablet CT-1 to CT-27

S. No.	F. Code	Angle of repose (θ)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's index (%)	Hausner's ratio
1	CT-1	31.33±0.075	0.447±0.0060	0.512±0.0020	12.695	1.145
2	CT-2	31.75±0.069	0.453±0.0011	0.519±0.0041	12.717	1.146
3	CT-3	31.58±0.075	0.484±0.0058	0.552±0.0030	12.319	1.140
4	CT-4	32.41±0.120	0.480±0.0023	0.549±0.0030	12.568	1.144
5	CT-5	30.68±0.069	0.487±0.0049	0.558±0.0017	12.724	1.146
6	CT-6	31.46±0.069	0.491±0.0023	0.565±0.0031	13.097	1.151
7	CT-7	32.32±0.140	0.452±0.0020	0.512±0.0039	11.719	1.133
8	CT-8	32.09±0.098	0.491±0.0036	0.565±0.0031	13.097	1.151
9	CT-9	32.33±0.069	0.505±0.0036	0.581±0.0033	13.072	1.150
10	CT-10	31.04±0.075	0.477±0.0013	0.553±0.0017	13.743	1.159
11	CT-11	31.01±0.106	0.488±0.0036	0.558±0.0017	12.545	1.143
12	CT-12	30.98±0.046	0.497±0.0024	0.571±0.0032	12.960	1.149
13	CT-13	31.25±0.125	0.440±0.0019	0.510±0.0026	13.725	1.159
14	CT-14	31.22±0.150	0.452±0.0020	0.529±0.0028	14.556	1.170
15	CT-15	31.83±0.075	0.456±0.0031	0.535±0.0028	14.766	1.173
16	CT-16	31.71±0.125	0.463±0.0032	0.543±0.0029	14.733	1.173
17	CT-17	32.49±0.120	0.480±0.0035	0.552±0.0030	13.043	1.150
18	CT-18	32.99±0.140	0.502±0.0038	0.574±0.0033	12.544	1.143
19	CT-19	33.14±0.120	0.476±0.0045	0.542±0.0034	12.177	1.139
20	CT-20	31.37±0.125	0.480±0.0023	0.552±0.0030	13.043	1.150
21	CT-21	31.91±0.125	0.506±0.0039	0.590±0.0053	14.237	1.166
22	CT-22	33.52±0.140	0.508±0.0051	0.595±0.0035	14.622	1.171
23	CT-23	34.06±0.136	0.512±0.0041	0.600±0.0075	14.667	1.172
24	CT-24	32.49±0.069	0.520±0.0024	0.612±0.0057	15.033	1.177
25	CT-25	31.75±0.125	0.490±0.0028	0.570±0.0049	14.035	1.163
26	CT-26	32.83±0.140	0.496±0.0014	0.579±0.0038	14.335	1.167
27	CT-27	31.58±0.125	0.502±0.0014	0.581±0.0033	13.597	1.157

Table 6: Depicted post-compression parameters of the core tablet batches (CT-1 to CT-27)

S. No.	F. code	Mean weight (mg)±SD, n-20	Weight variation (%)±SD, n-20	Thickness (mm)±SD, n-3	Crushing strength (kg/cm²)±SD, n-3	Friability (% loss)±SD, n-20	Dis.T (Sec.)±SD n-3	% Drug content
1	CT-1	93.29±1.160	0.877±1.243	3.056±0.051	3.03±0.173	0.710±0.003	76.33±0.57	90.91±0.15
2	CT-2	94.89±0.989	0.845±1.042	3.016±0.028	3.45±0.162	0.335±0.008	69.33±0.57	99.66±0.90
3	CT-3	96.64±1.610	1.344±1.666	3.083±0.020	2.96±0.156	0.593±0.007	83.66±1.52	92.75±0.52
4	CT-4	91.83±1.803	1.426±1.963	3.066±0.030	3.18±0.153	0.806±0.006	94.33±1.52	92.30±0.37
5	CT-5	92.84±1.423	1.184±1.533	3.053±0.047	3.13±0.156	0.711±0.005	100.33±1.15	92.90±0.18
6	CT-6	93.40±1.429	1.203±1.530	3.096±0.020	3.23±0.159	0.650±0.003	96.33±1.52	93.96±0.42
7	CT-7	90.65±1.214	1.075±1.339	3.086±0.020	3.03±0.163	0.606±0.005	78.33±0.57	95.08±0.25
8	CT-8	92.10±1.191	1.02±1.293	3.060±0.017	3.11±0.164	0.578±0.011	73.66±1.52	95.83±0.25
9	CT-9	92.75±1.342	1.159±1.447	3.050±0.030	2.96±0.167	0.629±0.006	75.66±0.57	96.36±0.11
10	CT-10	93.17±1.109	0.987±1.190	3.156±0.015	3.04±0.162	0.697±0.005	97.66±1.15	96.25±0.62
11	CT-11	95.01±1.399	1.065±1.473	3.180±0.017	3.08±0.162	0.727±0.002	83±1.0	97.16±0.16
12	CT-12	97.17±1.340	1.142±1.379	3.173±0.020	3.07±0.164	0.756±0.005	92.33±1.52	96.43±0.32
13	CT-13	92.05±0.723	0.613±0.786	3.146±0.040	2.97±0.164	0.452±0.002	107±2.64	97.65±0.50
14	CT-14	93.0±0.725	0.591±0.780	3.146±0.005	3.54±0.155	0.283±0.003	58.66±1.15	100.26±0.33
15	CT-15	93.9±1.231	1.075±1.311	3.186±0.015	3.11±0.135	0.480±0.001	96.66±1.52	95.25±0.52
16	CT-16	91.07±1.184	0.985±1.300	3.190±0.020	3.17±0.137	0.526±0.005	120.66±2.08	89.63±0.17
17	CT-17	92.07±1.016	0.765±1.104	3.150±0.020	3.03±0.142	0.571±0.002	107.66±0.57	91.06±0.10
18	CT-18	93.0±1.317	1.075±1.417	3.126±0.015	3.08±0.131	0.603±0.002	105.66±1.52	93.38±0.25
19	CT-19	97.88±0.893	0.657±0.912	3.036±0.020	3.15±0.122	0.890±0.002	75.0±2.0	92.08±0.10
20	CT-20	99.92±1.340	0.948±1.341	3.030±0.010	3.19±0.120	0.793±0.003	75.66±1.52	94.08±0.25
21	CT-21	101.87±0.971	0.711±0.953	3.070±0.020	3.23±0.121	0.726±0.004	79.0±1.0	94.85±0.25
22	CT-22	97.02±0.865	0.651±0.892	3.043±0.025	3.22±0.127	0.697±0.002	82.33±2.51	88.90±0.13
23	CT-23	97.97±0.834	0.643±0.851	3.043±0.015	3.22±0.129	0.607±0.005	89.33±1.52	89.75±0.18
24	CT-24	98.75±0.819	0.658±0.829	3.036±0.015	3.25±0.128	0.548±0.002	87.66±1.15	91.31±0.02
25	CT-25	96.27±0.834	0.631±0.866	3.036±0.037	3.31±0.121	0.425±0.005	74.33±1.52	94.10±0.32
26	CT-26	97.02±0.499	0.347±0.514	3.006±0.011	3.57±0.115	0.188±0.002	52.66±0.57	100.31±0.32
27	CT-27	97.97±0.952	0.696±0.972	3.043±0.020	3.36±0.011	0.401±0.003	76.66±1.52	95.15±0.22

of maximized acid neutralization capabilities of composite [Table 2]. The appraised micromeritics of granular blend was found to be excellent. The working blend of the granular composite was compressed on the rotary compression machine using 14 mm (spherical and concave shaped), die punch set. Based on investigation of post-compression parameters of outer tablet, it was observed that the OT-2 batch [Table 7], comprising microcrystalline cellulose as disintegrant, was best among rest of all batches (OT-1 to OT-9), with crushing strength of 5.55 ± 0.132 kg/cm², Friability 0.098 ± 0.004 (% loss), and disintegration time of 161.33 ± 0.57 s. The crushing strength of second finest batch, OT-5 was found to be 5.35 ± 0.102 kg/cm², Friability 0.184 ± 0.011 (% loss), and disintegration time of 182.33 ± 0.57 s. The crushing strength of third finest batch, OT-8 was found to be 5.41 ± 0.094 kg/cm², Friability 0.249 ± 0.011 (% loss), and disintegration time of 194.33 ± 0.57 s. The second finest batch (OT-5) among all, consisting of sodium starch glycolate as disintegrant and third finest batch (OT-8) consisting of HPMC as disintegrant, were additionally investigated in progressive development of formulation, tablet in tablet.

Compression and evaluation of post-compression parameters of tablet in tablet

On the bases of outcome of the investigation on post-compression parameters of core tablets (CT-1 to CT-27) and outer tablets (OT-1 to OT-9), three batches of tablet in tablet were developed and investigated. The description of various batches of tablet in tablet is depicted in Table 4. The core tablets (F. Code: CT-2, CT-14, and CT-26) were compressed with the previously formulated granules as per finalized composition on a rotary compression machine

using 6.5mm (spherical and concave shaped), die punch set. The final compression of tablet in tablet batches was realized by compressing the granules of respective outer tablet granules (F. code OT-8, OT-5, and OT-2) around core tablets (F. Code: CT-2, CT-14, and CT-26) on rotary compression machine using 14 mm (spherical and concave shaped), die punch set [Figure 2]. Tablet in tablet formulations were evaluated nearly on same stipulations and parameters as used for characterizing uncoated tablet [Table 8 and Table 9], additionally the core tablets were also evaluated on similar terms before subjecting to final compression of tablet in tablet formulation. The analysis of the entire tablet in tablet (T in T-1 to T in T-3) batches reveals that of the Tablet in Tablet -3 (T in T-3, comprising of CT-26 and OT-2) was the best batch, among rest of all batches (T in T-1 to T in T-3), with mean weight 776.95 ± 0.394 mg, thickness 6.516 ± 0.028 mm, crushing strength of 6.10 ± 0.276 kg/cm^2, Friability 0.193 ± 0.006 (% loss), disintegration time of 189.33 ± 0.577 s, and % drug content was found to be 97.36 ± 0.07.

In vitro release kinetics; release models

The Core tablet formulations (CT-1 to CT-27) were integrated in varied pharmacokinetic models, namely, zero-order, first-order, Higuchi, Hixson-Crowell, and Korsmeyer-peppas equation. The Korsmeyer-peppas kinetic plots were observed to be comparatively linear, signified by their utmost regression values (0.991) for CT-1 to CT-27 formulation. The release exponent "n" for formulation CT-1 to CT-27 was found to be 0.765 ($0.5 < n < 1$), that signifies inconsistent diffusion, that is, there was a blend of the diffusion and erosion mechanism. The drug release statistics of the tablet in tablet formulations (T in T-1 to T in T-3) were also integrated in varied pharmacokinetic models. The maximized regression values (0.991) for tablet in tablet formulations (T in T-1 to T in T-3) demonstrated the sensible linearity through Higuchi pharmacokinetic model, signifying the tablet in tablet formulations (T in T-1 to T in T-3) as modified release formulation.

Stability studies (accelerated stability studies) for the tablet in tablet formulations (T in T-1 to T in T-3)

Out of all, tablet in tablet (T in T-1 to T in T-3) formulations, the optimized formulation after accelerated stability studies (40°C ± 2°C/75% RH ± 5% RH) was found to be T in T-3, with mean weight (mg) 778.01 ± 0.024, Crushing strength (kg/cm^2) 6.122 ± 1.359, Disintegration Time (s) 195.21 ± 1.468, and % Drug content in 0.1 N HCl 96.79 ±0.539 [Table 10].

In vivo evaluation for optimized tablet in tablet formulation (T in T-3)

The HPLC was used to analyze the esomeprazole magnesium in rabbit blood plasma at varied time intervals. The samples were injected through rheodyne injector and the eluted

Table 7: Post-compression parameters of the outer tablets (OT-1 to OT-9)

S. No.	F.code	Mean weight (mg) ±SD, n-20	Weight variation (%)±SD, n-20	Thickness (mm) ±SD, n-3	Crushing strength (kg/cm^2) ±SD, n-3	Friability (% loss) ±SD, n-20	Dis.T (s)±SD n-3
1	OT-1	655.35±8.04	0.888±1.195	5.13±0.152	5.23±0.125	0.389±0.007	199.33±1.52
2	OT-2	677.15±6.64	0.777±0.981	5.03±0.057	5.55±0.132	0.098±0.004	161.33±0.57
3	OT-3	704.4±6.80	0.755±0.966	5.15±0.050	5.19±0.091	0.459±0.010	196.66±2.08
4	OT-4	654.85±7.84	0.749±1.197	4.15±0.050	5.23±0.094	0.460±0.011	202.66±0.57
5	OT-5	658.7±8.11	0.960±1.232	4.20±0.050	5.35±0.102	0.184±0.011	182.33±0.57
6	OT-6	664.9±6.76	0.723±1.017	4.10±0.050	5.17±0.105	0.526±0.007	196.66±1.15
7	OT-7	659.05±7.89	0.858±1.198	4.33±0.057	5.16±0.110	0.561±0.007	208.33±1.52
8	OT-8	667.85±10.61	1.134±1.589	4.36±0.057	5.41±0.094	0.249±0.011	194.33±0.57
9	OT-9	677.7±9.22	1.007±1.360	4.40±0.100	5.24±0.020	0.442±0.007	205.33±1.52

Table 8: Evaluation of the post compression parameters of the tablet in tablet

S. No.	F.Code	Mean weight (mg) ±SD, n-20	Weight variation (%)±SD, n-20	Thickness (mm) ±SD, n-3	Crushing strength (kg/cm^2) ±SD, n-3	Friability (% loss) ±SD, n-20	Disintegration Time (Sec.) ±SD, n-3	% Drug content in 0.1 N HCl
1	TinT-1	764.91±0.808	0.079±0.105	6.05±0.050	5.98±0.331	0.358±0.019	219.33±1.527	93.90±0.05
2	TinT-2	753.4±1.659	0.115±0.220	5.533±0.057	5.88±0.303	0.276±0.003	208±1.0	95.33±0.07
3	TinT-3	776.95±0.394	0.035±0.050	6.516±0.028	6.10±0.276	0.193±0.006	189.33±0.577	97.36±0.07

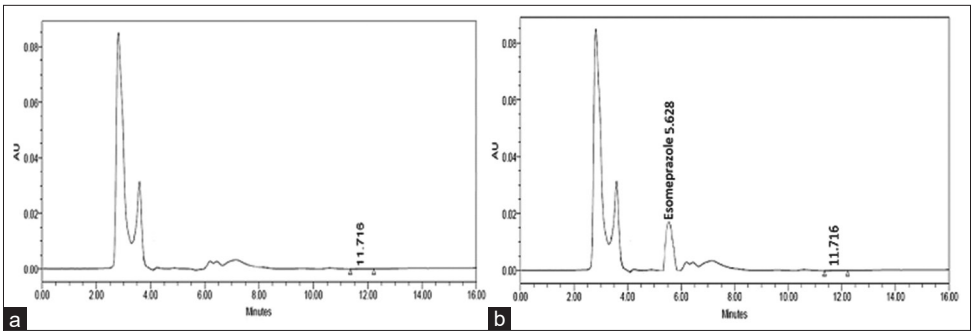

Figure 3: Chromatogram – (a) Blank (in plasma), (b) Esomeprazole magnesium (in plasma)

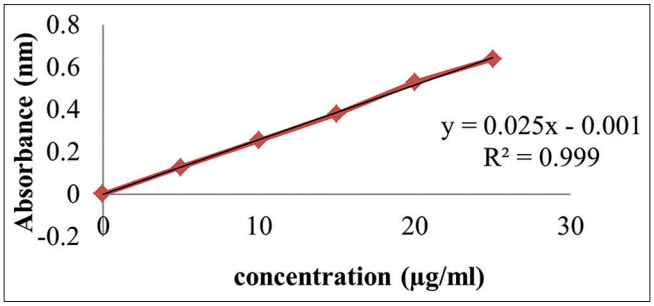

Figure 4: Standard plot of esomeprazole magnesium at 301 nm in plasma

Table 9: % cumulative drug released from tablet in tablet

Time (in min)	% cumulative drug release		
	TinT-1	TinT-2	TinT-3
5	9.96±0.12	10.10±0.05	10.83±0.02
10	20.88±0.05	22.85±0.10	24.81±0.10
15	37.30±0.05	38.90±0.05	40.30±0.13
20	54.88±0.07	56.30±0.13	58.90±0.05
25	67.83±0.10	69.33±0.12	71.26±0.20
30	80.78±0.12	81.68±0.15	83.81±0.18
35	89.35±0.10	90.15±0.05	92.31±0.15
40	93.90±0.05	95.33±0.07	97.36±0.07

components were detected by UV detector at 301 nm. The Chromatogram of Esomeprazole Magnesium and blank was taken in plasma [Figure 3] and standard plot was constructed [Figure 4].

Determination and analysis of pharmacokinetic parameters

The plasma level data from each rabbit were used to establish and analyze the pharmacokinetic parameters, which were exhibited as (±) mean standard deviation. The maximum plasma concentration (Cmax, µg/mL) and the corresponding time (Tmax, hour) for the two treatments in each rabbit were estimated through the plasma concentration data [Table 11]. The plasma concentration against time profiles after oral administration of the optimized formulation T in T-3 and marketed formulation has been presented in Figure 5. After administration of optimized formulation T in T-3, T_{max} was found to be 1.54 ± 0.19, which was significantly distinct ($P < 0.05$) from the 3.61 ± 0.77 T_{max} obtained from the enteric coated commercial formulation. The observed mean C_{max} for optimized formulation, T in T-3 (0.68 ± 0.98 mg/mL) was higher than that obtained from the enteric coated commercial formulation (0.56 ± 0.37 mg/mL). The peak area ratio versus concentration curve is presented in Figure 6. The MRT was 3.78 h for the optimized formulation and the AUC was 2.912 ± 1.53µg/mL/h. From the *in vitro* dissolution studies, it was found that the maximum drug release was achieved in about 60 min. Hence, from the *in vitro* and *in vivo* results it was evident that the release of esomeprazole from the optimized (T in T-3) formulation was quicker than the conventional commercial formulation. F_R (%) was found to be 91.861%.

DISCUSSION

Tablets are the most extensively used formulation amidst all dosage forms because of its precise dosing, convenience to use, and low cost.[11] The tablet in tablet is a step ahead, innovative technique and pragmatic tableting approach, where a tablet is compressed with a core tablet in the center. This technique may serves as coating over the core tablet but offer multiple advantages over conventional pan coating technique. The key benefit of this technology is, exclusion of water/solvent during coating, thus there is no core softening or undesirable initiation of chemical reaction, because of water/solvent penetration into the core tablet.[12] The core tablet is coated by compression in single step thus eliminating various time consuming steps (diverse alternative steps of coating and drying) followed during conventional pan coating.[12] The present research was an attempt to develop a unique modified immediate release formulation in which both API's (in core and in outer tablet) work in synergy and produce meaningful pharmacological outcome in gastritis and allied gastric disorders besides improving patient compliance.

In the development phase of formulation composition, for the outer tablet, the F-1 to F-11 purposed compositions of known components, possessing the acid neutralizing capabilities

Table 10: Physicochemical characterization of Tablet in Tablet (T in T-1 to T in T-3) at accelerated stability testing conditions (40°C±2°C/75% RH±5% RH) after 12 weeks

S. No.	Physico chemical characteristics	T in T-1 (after 12 weeks)	T in T-2 (after 12 weeks)	T in T-3 (after 12 weeks)
1.	Physical appearance	Color-Tatrazine, Spherical, convex top and bottom, smooth surface without any flaws or cracks	Color-White, spherical convex top and bottom smooth surface, without any flaws or cracks	Color-Sunset yellow, spherical, convex top and bottom, smooth surface, without any flaws or cracks
2.	Mean weight (mg)±SD, n-20	769.27±0.67	754.7±9.093	778.01±0.024
3.	Weight variation (%)±SD, n-20	0.207±0.710	0.129±0.862	0.127±0.010
4.	Thickness (mm)±SD, n-3	6.06±0.339	5.568±0.917	6.53±0.017
5.	Crushing strength (kg/cm^2) ±SD, n-3	6.21±0.729	6.13±0.103	6.122±1.359
6.	Friability (% loss)±SD, n-20	0.355±0.923	0.270±0.863	0.188±2.072
7.	Disintegration time (s)±SD, n-3	245.86±2.77	225.98±0.993	195.21±1.468
8.	% Drug content in 0.1 N HCl	90.33±1.35	89.94±0.947	96.79±0.539

Table 11: The evaluated pharmacokinetic parameters of optimized formulation and commercial enteric coated formulation in rabbit plasma

Parameters	Optimized formulation (TinT-3)	Enteric coated (marketed)
C_{max} (mg/mL)	0.68±0.98	0.56±0.37
T_{max} (h)	1.54±0.19	3.61±0.77
AUC_{total} (µg/mL/h)	2.912±1.53	3.17±1.31
$T_{1/2}$	2.08±0.21	3.25±1.45
MRT (h)	3.78±0.09	4.48±0.67

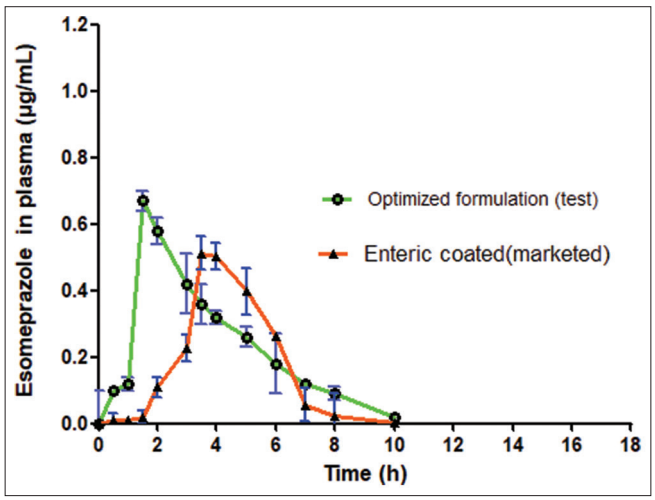

Figure 5: Plasma concentration versus time profile curve for TinT-3 and commercial formulation

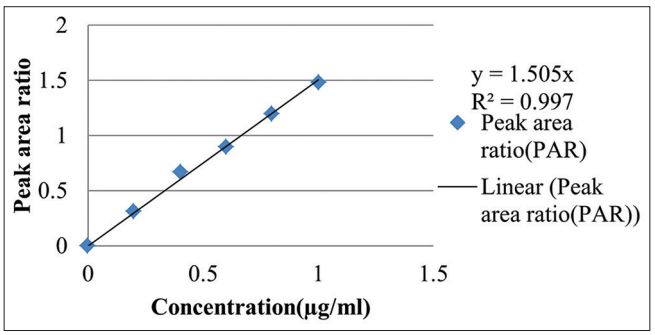

Figure 6: Peak area ratio versus concentration curve

were evaluated. The acid neutralization capability was measured by the Rossett-Rice test through the process of back titration. During the course of investigation, the F-9 batch was found to be the optimum composition with excellent neutralization capabilities of 8.107 mmol H+/g of acid neutralizing formulation. The batch composition formulas for outer tablet (OT-1 to OT-9) were prepared from the batch with best acid neutralizing capabilities (F-9).

Possible drug-excipient interactions between Esomeprazole Magnesium and Formulation constituents/excipients were envisaged through FTIR Spectrophotometric technique. All IR spectrums were interpreted for identification of compounds and blends were found to be compatible. The batch composition formulas (CT-1 to CT-27) for core tablet were prepared based on drug-excipients compatible studies. The micromeritic properties of the granular blend were appraised and the flow properties were found to be good. The final working granular blends were compressed on rotary compression machine using 6.5mm (spherical and concave shaped), die punch set. The post-compression parameters of the core tablets revealed that the CT-26 batch, comprising of polyethylene glycol as binder and sodium starch glycolate as disintegrant,

was best among rest of all batches (CT-1 to CT-27), with crushing strength of 3.57 ± 0.115 kg/cm^2, Friability 0.188 ± 0.002 (% loss), disintegration time of 52.66 ± 0.57 s, and % drug content was found to be 100.31 ± 0.32. The crushing strength of second finest batch, CT-14 was found to be 3.54 ± 0.155 kg/cm^2, Friability 0.283 ± 0.003 (% loss), disintegration time of 58.66 ± 1.15 s, and % drug content was found to be 100.26 ± 0.33. The crushing strength of third finest batch, CT-2 was found to be 3.45 ± 0.162 kg/cm^2, Friability 0.335 ± 0.008 (% loss), disintegration time of 69.33 ± 0.57 s, and % drug content was found to be 99.66 ± 0.90. The second finest batch (CT-14) among all, consisting of Acacia as binder and HPMC as disintegrant and third finest batch (CT-2) consisting of polyvinyl pyrrollidone as binder, and microcrystalline cellulose as disintegrant, was additionally investigated in progressive development of formulation, tablet in tablet.

The batches of outer tablet (OT-1 to OT-9) were prepared by wet granulation method using hydrolyzed starch paste as binder. The micromeritic properties of the granular blend were appraised and the flow properties were found to be excellent. The final working granular blends were compressed (devoid on core tablet) on rotary compression machine using 14 mm (spherical and concave shaped), die punch set. The post-compression parameters of outer tablet, reveals that the OT-2 batch, comprising of microcrystalline cellulose as disintegrant, was best among rest of all batches (OT-1 to OT-9), with crushing strength of 5.55 ± 0.132 kg/cm^2, Friability 0.098 ± 0.004 (% loss), and disintegration time of 161.33 ± 0.57 s. The crushing strength of second finest batch, OT-5 was found to be 5.35 ± 0.102 kg/cm^2, Friability 0.184 ± 0.011 (% loss), and disintegration time of 182.33 ± 0.57 s. The crushing strength of third finest batch, OT-8 was found to be 5.41 ± 0.094 kg/cm^2, Friability 0.249 ± 0.011 (% loss), and disintegration time of 194.33 ± 0.57 s. The second finest batch (OT-5) among all, consisting of sodium starch glycolate as disintegrant and third finest batch (OT-8) consisting of HPMC as disintegrant, was additionally investigated in progressive development of formulation, tablet in tablet.

On the bases of outcome of the post-compression parameter investigations of the core tablets (CT-1 to CT-27) and outer tablets (OT-1 to OT-9), three batches of tablet in tablet were developed and explored. The core tablets (F. Code: CT-2, CT-14, and CT-26) were compressed with the previously formulated granules as per finalized composition on a rotary compression machine using 6.5 mm (spherical and concave shaped), die punch set. The final compression of tablet in tablet batches was realized by compressing the granules of respective outer tablet granules (F. code OT-8, OT-5, and OT-2) around core tablets (F. Code: CT-2, CT-14, and CT-26) on rotary compression machine using 14 mm (spherical and concave shaped), die punch set. All the three batches of tablet in tablet (T in T-1 to T in T-3) were evaluated for post compression parameters **(**mean weight, weight variation, Thickness, crushing strength, friability, disintegration time, % drug content, and % cumulative drug release). The analysis of the entire tablet in tablet (T in T-1 to T in T-3) batches reveals that of the tablet in tablet -3 (T in T-3, comprising of CT-26 and OT-2) was the best batch, among rest of all batches (T in T-1 to T in T-3), with mean weight 776.95 ± 0.394 mg, thickness 6.516 ± 0.028 mm, crushing strength of 6.10 ± 0.276 kg/cm^2, Friability 0.193 ± 0.006 (% loss), disintegration time of 189.33 ± 0.577 s, and % drug content was found to be 97.36 ± 0.07.

The *in vitro* release of Esomeprazole magnesium from varied tablet in tablet formulations were also assessed by integrating drug release statistics into diverse release pharmacokinetics models. The maximized regression values (0.991) for Tablet in Tablet formulations (T in T-1 to T in T-3) demonstrated the sensible linearity through Higuchi pharmacokinetic model, signifying the tablet in tablet formulations (T in T-1 to T in T-3) as modified release formulation.

The tablet in tablet formulations (T in T-1 to T in T-3) were subjected to short term accelerated stability studies as per ICH guidelines and protocol. The T in T-3 was found to be the optimum formulation with consistent sunset yellow color; the surface was smooth without any flaws or cracks. No change was observed in the physical appearance at the end of 12th week. The other observed parameters at the end of study were; mean weight 778.01 ± 0.024 mg, thickness 6.53 ± 0.017 mm, crushing strength of 6.122 ± 1.359 kg/cm^2, friability 0.188 ± 2.072 (% loss), disintegration time of 195.21 ± 1.468 s, and % drug content was found to be 96.79 ± 0.539. The evaluated physical parameters; namely, mean weight, thickness, crushing strength, friability, and disintegration time for all of the tablet in tablet formulations (T in T-1 to T in T-3) were in acceptable limits but the % drug content of the T in T-1 and T in T-2 falls drastically, suggested sudden deterioration in T inT-1 and T inT-2 formulations beyond acceptable limits and appropriateness of T inT-3 formulation for further *in vivo* investigations.

In the *in vivo* pharmacokinetic evaluation, the optimized tablet in tablet (T in T-3) formulation was compared with the commercially accessible enteric coated Esomeprazole caplet (Nexpro 20 mg manufactured by Torrent Pharmaceuticals limited). The HPLC was used to analyze the esomeprazole magnesium in rabbit blood plasma at varied time intervals. The maximum plasma concentration (C_{max}, µg/mL) and the corresponding time (T_{max}, hour) for the two treatments in each rabbit were estimated. The T_{max} was found to be 1.54 ± 0.19, which was significantly distinct ($P < 0.05$) from the 3.61 ± 0.77 T_{max} obtained from the enteric coated commercial formulation. The observed mean C_{max} for optimized formulation, T in T-3 (0.68 ± 0.98 mg/mL) was higher than that obtained from the enteric coated commercial formulation (0.56 ± 0.37 mg/mL). The MRT was 3.78 h and the AUC was 2.912 ± 1.53µg/mL/h for the optimized formulation. From the *in vitro* dissolution studies it was found that the maximum drug release was achieved in about 60 min. Hence, from the *in vitro* and *in vivo* results, it was evident that the release of

esomeprazole from the optimized (T in T-3) formulation was quicker than the conventional commercial formulation with relative bioavailability (F_R %) 91.861%

CONCLUSION

The tablet in tablet technology is an exceptionally promising formulation technique which is conventionally used to manufacture Sustained release, Control release, and Delayed release tablet formulation but in the present study this technology was used to formulate an immediate release formulation, in which Esomeprazole Magnesium; an acid labile drug was kept in core tablet and the outer tablet confining acid neutralizing agents. The constituents of core tablet and outer tablet release simultaneously in the stomach acidic environment. The outer tablet containing acid neutralizing agents counterbalance the gastric environment and thus providing favorable pH environment for the release of esomeprazole in stomach. Both the constituents act in synergy to produce desired pharmacological action. This will provide instantaneous relief with the release of acid neutralizing agents from the outer tablet and proffer prolong relief (with the release of esomeprazole from the core table) from the gastric symptoms due to irreversible binding to cysteine residues of the H^+/K^+ATPase. The clinical action of each drug component will not alter and exhibited their action in synergy. This will offer better therapeutic efficacy and improve patient compliance. In addition, if the formulation is required to be commercialized in future, the size of the formulation shall essentially be optimized, to 12 mm. Due to the available resources; the final tablet in tablet formulation was prepared on 14 mm die-punch set, which may cause difficulty in swallowing in certain population. The quantity and contents of the optimized tablet in tablet formulation can easily be compressed to 12 mm, without significant increment in thickness. There are certain additional considerations to be taken while developing any formulation in tablet in tablet dosage form. Ideally, the weight of outer tablet granules must be kept twice in weight to that of a core tablet (if they comprise comparable densities). If the constituents of outer tablet comprised of lighter density to core then the volume is to taken in consideration. Roughly the tapped volume of outer tablet granules must be twice or more in comparison to the tapped volume, of a core tablet. The core tablet must be kept as small as possible. The outer tablet granules must possess cohesiveness and plasticity to produce a physically stable formulation. The shape of core tablet used to constitute tablet in tablet is of considerable importance. Ideally tablet in tablet, constituting core tablet and outer tablet must be convexed shaped, for proper centration of the core tablet in the outer tablet. It can also be formulated with flat tablet punches but may have additional processing complications, that is, improper centration, namely, unequal position, cocking or off centered core in outer tablet. It can be eliminated by optimizing formulation composition and reducing compression speed.

AUTHORS DISCLOSURE STATEMENT

The authors have no conflict of interest to disclose.

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