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Research

Formulation Development and Evaluation of Tablet Dosage Form for Quick and Protracted Relief in Gastritis and Allied Gastric Disorders

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Abstract:

Objective: The object of the current study was to evaluate the tablet's uniqueness in tablet composition with the belief that it would provide both immediate and long-term relief from gastritis and related stomach problems. **Method:** It was intended to match the batch composition formulae for the core tablets to the potential drug-excipient interaction between Esomeprazole Magnesium and the formulation constituents/excipients of the core and outer tablet. The outer tablets and core tablets were squeezed using a 6.5 mm die punch (concave) set. (without core tablet) were crushed with a 14 mm concave die punch that was adjusted to the ideal compression load and speed. Three batches of tablets were purposed and compressed based on the performance results of the core and outside tablet batches. These batches were then exposed to in vitro release kinetics during the evaluation of the post compression parameters. To predict how the environment would affect the final formulation's quality and to make sure that no changes had been made to the formulation during the manufacturing process, short-term accelerated stability testing of the various tablet batches in tablet formulations was carried out. things can have an adverse effect on its stability. **Result and conclusion:** With a crushing strength of 3.57, the batch which included sodium starch glycolate as a disintegrant and polyethylene glycol as a binder was the best of all the batches (CT-1 to CT-9), according to the post-compression characteristics of the core tablets. ± 0.115 kg/cm2, a disintegration time of 52.66 ± 0.57 s, a Friability of 0.188 ± 0.002 (percent loss), and a drug content of 100.31 ± 0.32. Out of all batches (OT-1 to OT-9), the OT-2 batch, which contained microcrystalline cellulose as the disintegrant, outperformed the others according to the post-compression parameters of the outer tablet. Its crushing strength was 5.55 ± 0.132 kg/cm2, its friability was 0.098 ± 0.004 (percent loss), and its disintegration time was 161.33 ± 0.57 seconds.

Keywords: Esomeprazole Magnesium, gastritis, formulation, stability and excipient.

1. INTRODUCTION

Due to their better acid suppression, proton pump inhibitors (PPIs) are commonly advised to treat a variety of hypergastrinemic problems. safety as well as patient approval Since all PPIs are weak, acid-labile bases, they are enteric coated to slow the breakdown of the medicine in the stomach. [1] Sodium bicarbonate is usually included to PPI formulations in order to temporarily raise pH and stop medication breakdown in lower pH

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environments. Additionally, sodium bicarbonate promotes gastrin release, which in turn triggers the H+/K +ATPase pump.

Esomeprazole is allowing for the quick suppression of acid production. [2] They are mostly prodrugs that, after building up in canaliculi, activate the sulfenic acid and sulfonamide moiety of a parietal cell that is activated. Here, they form an irreversible, covalent bond with the cysteine residues on the H+/K+AT's alpha subunit. For up to 36 hours, pass via disulfide bonds and limit the creation of acid. [3] In the liver, cytochrome P450 isozymes CYP2C19 and CYP3A4 extensively metabolize all PPIs. [4,5]

A novel and practical method is tablet in tablet, in which a tablet is compressed with a core tablet in the middle. [6] Put otherwise, the outer tablet entirely encloses the inner tablet. Another way to describe it is as a compression-coated tablet, in which the outer tablet serves as a coating for the inner tablet. [7] By putting such acid-labile drugs in core tablets, drug breakdown at the lower pH in the stomach can be avoided. [8] Some medications, such as non-steroidal anti-inflammatory drugs, are known to cause gastric irritation. By putting these medications' ingredients in the core tablet, the outer tablet will function as a barrier, preventing the irritant medication from coming into direct contact with the stomach. [9] In addition to enhancing patient compliance, the current study aimed to create a novel modified immediate release formulation in which the two APIs (in the core and outside tablet) function in concert to provide significant pharmacological results in gastritis and related stomach illnesses.[10]

2. MATERIALS AND METHOD

Synokem Pharmaceutical Industries Ltd., Paonta Sahib, Himachal Pradesh, India, provided the Esomeprazole Magnesium (IP) as a gift sample. All other excipients and ingredients, whether analytical or laboratory grade, were purchased from a local supplier.

2.1 Pre-formulation Study

2.1.1 Identification of Esomeprazole Magnesium through Melting point

As per pharmacopoeial test protocol, the melting point was determined at the inception and completion of melt [11]. It was determined as per protocol given in USP25-NF20 US Pharmacopeia. The Temperature was recorded when Esomeprazole Magnesium in the capillary tube begins to melt and the temperature at which the drug was completely molten and become transparent [12] The average, triplicate readings were recorded.

2.1.2 Identification of Esomeprazole Magnesium by FTIR

The identification of the pure Esomeprazole Magnesium was established through FT IR spectrophotometric technique, through identification of different functional groups present in drug sample. The Esomeprazole Magnesium - potassium bromide pellet was analyzed under the FTIR spectrophotometer under a scanning range between 4000 cm-1 - 400 cm-1 at a resolution of 4 cm-1 9 [13] The peaks obtained in the spectrum were characteristic of a particular functional group, which were used to establish the identity of Esomeprazole Magnesium.

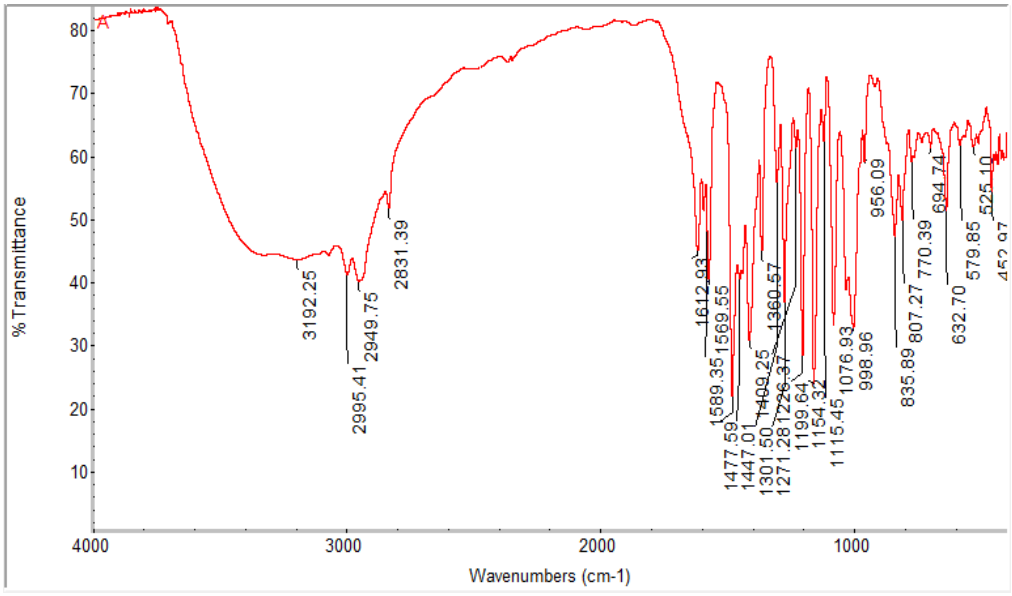

Fig 3 FTIR Spectra Esomeprazole Magnesium

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2.1.3 Identification of Esomeprazole Magnesium by HPLC

The Reverse-phase HPLC was used to carry out analytical determination of Esomeprazole Magnesium. For stationary phase C-18 column was used (Kromasil 100-5-C18; column length 250 mm, 4.6 mm internal diameter & 5.0 µm particle size of silica) and for isocratic mobile phase solution of acetonitrile & methanol in ratio 50:50 (v/v) were considered [14]. They were filtered through a 0.22 µm millipore membrane filter and degassed for 15 minutes on a bath sonicator [15] The standard stock solution was prepared by introducing 10 mg of Esomeprazole Magnesium in a 10 ml volumetric flask. The Methanol was added; Q.S to make 10ml. At this stage, the concentration of the solution was 1000 µg/ml. This solution was termed; stock Solution-A. 5 ml of this stock Solution-A was diluted to 50 ml with methanol to make a working dilution of concentration 100 µg/ml; in a 50 ml volumetric flask. This solution was termed; stock Solution-B. 1ml from working stock Solution–B was then taken in a 10 ml volumetric flask. The rest of the volume was made using methanol, which constitutes the concentration of this solution to 10 µg /ml This solution (concentration 10 µg/ml) was used to analyze and identify Esomeprazole magnesium through HPLC. The volume of solution injected; was 20 µL. The flow rate of the mobile phase was kept at 1 ml/min. Column temperature was 25 0C [16]. The Run time was kept up to 10 minutes. The sample was scanned through a maximum.

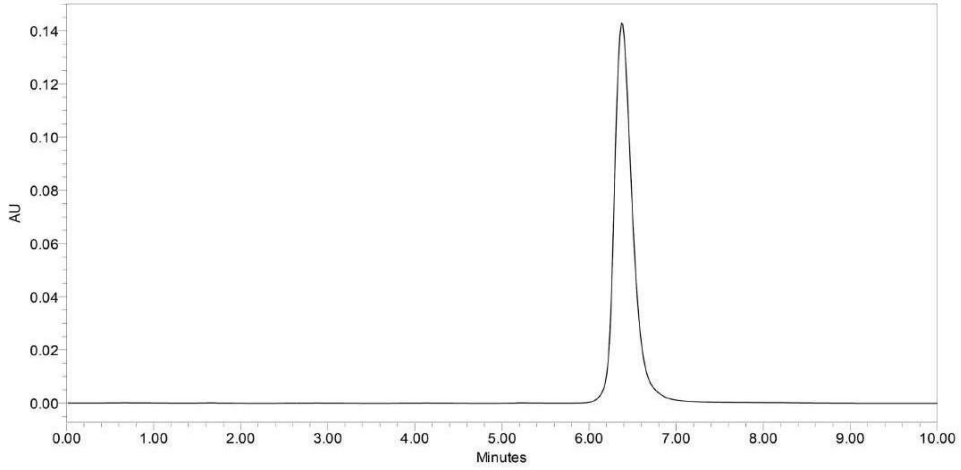

Fig.2. Chromatogram of Esomeprazole Magnesium

2.1.4 Calibration curve of Esomeprazole Magnesium and determination of λ Max for the quantitative estimation

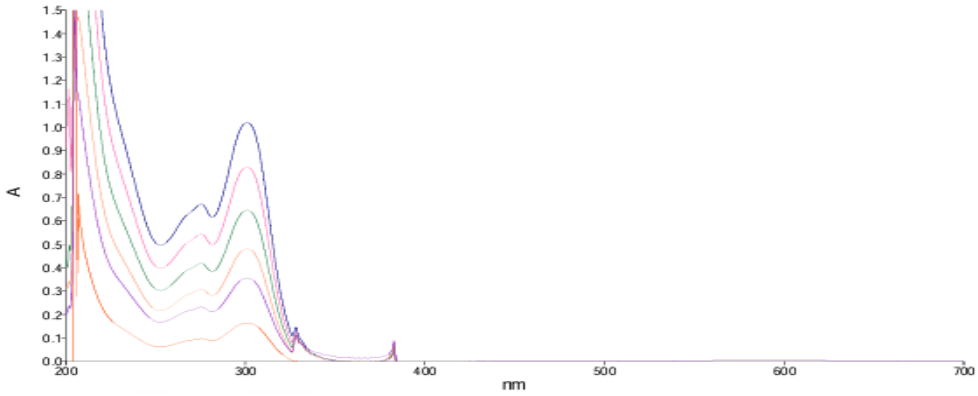

Fig. 3. Linearity spectra of Esomeprazole Magnesium at 301nm in phosphate buffer (pH-6.8)

2.1.5 Assessment of Particle size (Optical Microscopy and Malvern Zetasizer)

The particle size of Esomeprazole Magnesium was also determined through Malvern Zetasizer. The diluent used for the assessment was water. The drug particle suspension was kept at 25.1 0C for 5 minutes to ensure temperature consistency in the test sample. The refractive index was 1.3328 and viscosity was 0.8858 cP with scattering intensity 8951cps [17]. These values were used to predict intensity distribution, volume distribution, and number distribution.

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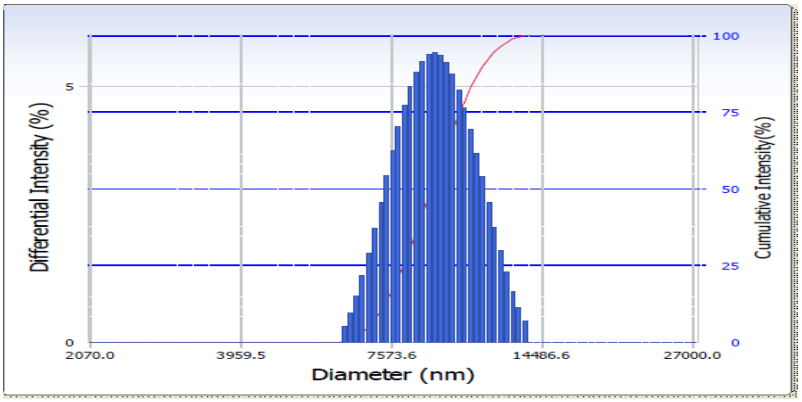

Fig.4. Intensity distribution of Esomeprazole Magnesium by Malvern Zetasizer

2.1.6 Solubility study of drug (Esomeprazole Magnesium) in different solvent systems

The solubility of Esomeprazole Magnesium was determined by UV spectrophotometric analysis. The medium chosen were distilled water, methanol, 0.1 N HCl, phosphate buffer (pH-6.8 & pH-7.4), and simulated gastric & intestinal fluids (pH-1.2 & pH-6.8 respectively). The standard curve of Esomeprazole Magnesium was prepared in experimental solvents at 301 nm. The saturated solution of Esomeprazole Magnesium in the experimental solvents was prepared by adding an excess amount of Esomeprazole Magnesium in 10 ml volumetric flasks with occasional shaking for 2 hours at ambient temperature. The solubility of Esomeprazole Magnesium was determined and tabulated.

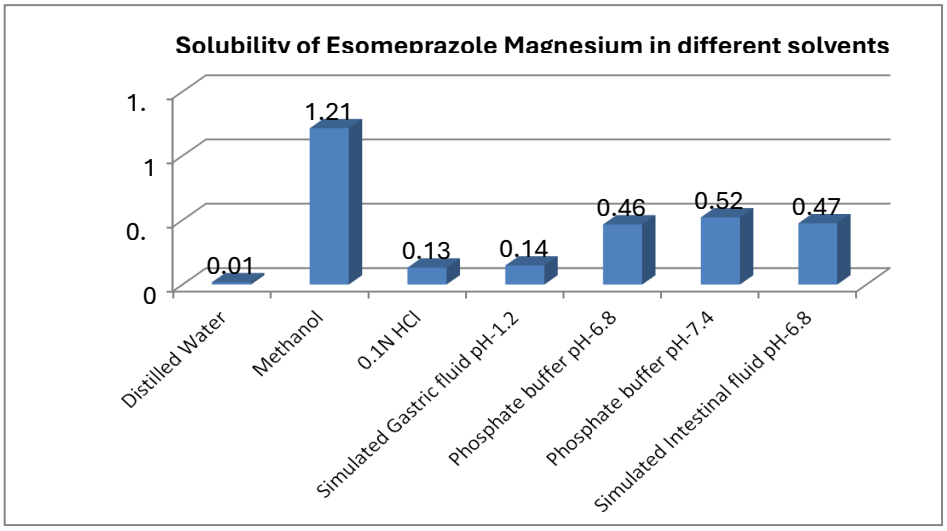

Fig 5: Solubility of Esomeprazole Magnesium in different solvents (mg/ml)

2.2 Preparation of preliminary granular blend for the core tablets.

The core tablets were prepared through double compression except batches CT-1 to CT-9, which was supplemented with polyvinyl pyrrollidone as binder. The isopropyl alcohol was added to polyvinyl pyrrollidone, and thus CT-1 to CT-9 batches was formulated through wet granulation technique.

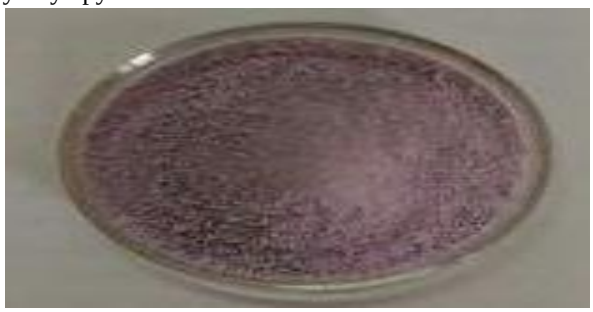

Fig 6: granular blend for the core tablets

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2.3 Compression of Core Tablets

The final working granules were compressed on rotary compression machine using 6.5mm (spherical and concave shaped), die punch set. The compression speed and compression load was 3.5 RPM and 3.8 tons respectively.

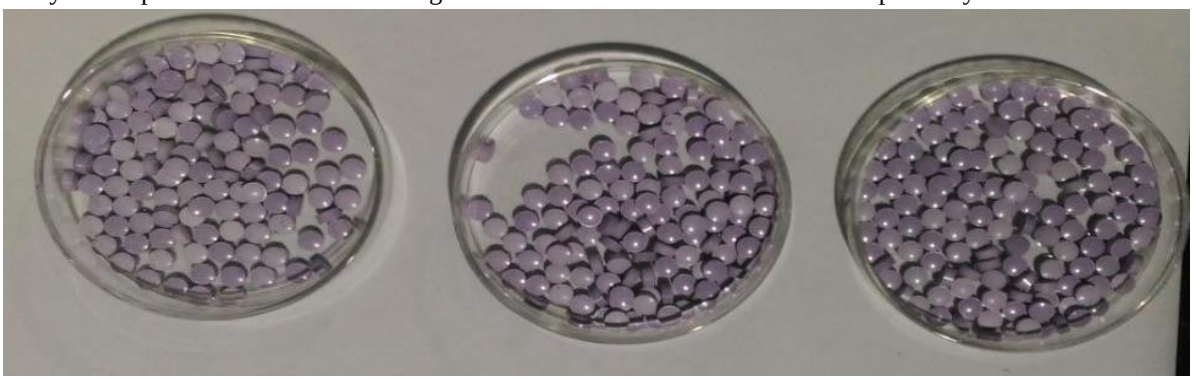

Fig 7: compressed core tablets

3. Evaluation of post-compression parameters of the core tablets

3.1 Mean weight and weight variation:

Randomly 10 tablets were selected from a particular batch and weighed in isolation and also amalgamatedly. The average mass of tablet was calculated by dividing the composite weight of sample tablets by number of tablets in the sample. The weight variation assessment was performed by comparing the average weight of the tablets to the weight of individual tablets. Not more the one tablet should fall out of USP weight variation tolerance limits **3.2 Thickness:** The dimensional thickness of the core tablets were estimated using vernier caliper and it should not be ± 5 % of the standard value

3.3 Crushing strength: The crushing strength of the core tablets were determined by placing the core tablet diametrically between upper and lower plungers of the Monsanto hardness tester. The crushing strength was reported from the pointer on the scaled barrel of the Monsanto hardness tester [18].

S.No.	F. Code	Mean Weight (mg)±SD,n-20	Weight variation (%)±SD, n-20	Thickness (mm)±SD,n-3
1	CT-1	93.29±1.160	0.877±1.243	3.056±0.051
2	CT-2	94.89±0.989	0.845±1.042	3.016±0.028
3	CT-3	96.64±1.610	1.344±1.666	3.083±0.020
4	CT-4	91.83±1.803	1.426±1.963	3.066±0.030
5	CT-5	92.84±1.423	1.184±1.533	3.053±0.047
6	CT-6	93.40±1.429	1.203±1.530	3.096±0.020
7	CT-7	90.65±1.214	1.075±1.339	3.086±0.020
8	CT-8	92.10±1.191	1.02±1.293	3.060±0.017
9	CT-9	92.75±1.342	1.159±1.447	3.050±0.030

3.4 Friability: The Roche friabilator was employed to investigate the friability of respective batch of core tablets by placing 20 compositely weighed core tablets in the spherical chamber which was allowed to spin for 100 revolutions in four minutes. The weight loss of the core tablets was reported which ideally should be less than 1% of the average weight of the composite core tablets

3.5 Disintegration time: The disintegration time was measured through USP disintegration test apparatus by placing the core tablet, one in each of 6 tubes of the disintegration test assembly placed in phosphate buffer with pH 6.8 maintained at 37 0C ± 2 0C. The time taken by the core tablets to pass

through the 10 mesh sieve was tabulated and reported.

3.6 Dissolution time and cumulative drug release: The dissolution time was estimated using USP 8 station dissolution test apparatus type-2 (Paddle type) maintained at 37 0C ± 2 0C. The phosphate buffer (pH 6.8) was used as dissolution medium. The USP dissolution test apparatus type-2 (Paddle type) was kept and maintained at constant settings (RPM/Temp.) for one hour before commencing the test. The core tablets were introduced to each hemispherical flask and paddles were allowed to rotate at 50 RPM. The sample liquates were withdrawn at prefixed time intervals and replaced by same.

CONCLUSION

In the preliminary investigation phase, the blank Tablet in Tablet formulation (Trial formulation) was prepared to envisage the viability of the project under available resources. The conventional 10 station rotary pilot press was used to compress core tablet containing calcium carbonate by employing wet granulation method. The compression of the nuclear tablets was executed by employing 8 mm die and concave punch set. The outer tablets were compressed around core with 12mm die and flat punch set to finalize the Tablet in Tablet formulation. Physically the Trial formulation (Tablet in Tablet formulation) was acceptable but it was noticed experimentally that the concave punches would have been better for proper centration of core tablet.

The API in core tablet (Esomeprazole magnesium) was qualitatively and quantitatively portrayed by considering varied analytical & investigative approaches and tools. It was discovered that the Esomeprazole magnesium was off-white, amorphous powder with a distinct, unpleasant smell and a somewhat bitter taste. The identification model drug contender (esomeprazole) was done by employing diverse investigative techniques viz HPLC, melting point etc. The λ max was predicted at 301 nm, employing UV spectrophotometric and HPLC analysis. The API was also identified through FTIR, through the classification of characteristic peaks of functional groups in the IR spectra. melting point corresponds to literature statistics. The particle size of the API under test was investigated by employing Malvern zetasizer and also through conventional optical microscopy. The particle size was predicted as 11.818 µm, when explored through Malvern zetasizer..

The batch composition formulas for core tablet were prepared based on drug-excipients compatible studies. They were further distinguished with the aid of color comprising of particular binder in the formulation. The batches comprising polyvinyl pyrrollidone as a binder was supplemented with brilliant blue dye to distinguish it from rest of batches containing dissimilar binder. The core tablets were prepared through double compression except batches which was supplemented with polyvinyl pyrrollidone as binder. The isopropyl alcohol was added to polyvinyl pyrrollidone, and thus batches was formulated through wet granulation technique. The slugs of respective batches were prepared on 14 mm die-punch set and randomly crushed in mortar and passed through sieve no 12, to acquire required preliminary granules (retained over sieve no16). The undersized granules were again compressed using 14 mm die punch set, to get slugs for required quantity of granules. The initial granules obtained after passing the pulverized slugs through sieve no 12, were further passed through sieve no 22 to get ideal granular size for compression. The residual ingredients of the formulation were incorporated to the final granules. The micromeritic properties viz. angle of repose, density (Bulked and Tapped density), Carr's index, and Hausner's ratio of the granular blend were appraised and the flow properties were predicted as good. The final working granular blends were compressed on rotary compression machine using 6.5mm (spherical and concave shaped), die punch set.

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