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Formulation And Evaluation Of Esomeprazole Magnesium Controlled Release Multiple Unit Matrix Pellets By Extrusion And Spheronization Technology

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Abstract: ***Esomeprazole magnesium trihydrate is a proton pump inhibitor which reduces acid secretion through the inhibition of H^+/K^+ ATPase in gastric parietal cell. Esomeprazole is the S-isomer of omeprazole. The present study was an attempt made to formulate and evaluate esomeprazole enteric coated matrix pellets by Extrusion and Spheronization method using HPMC, Xanthan gum as control release polymers. Pellets are filled in the enteric coated capsules which were not disintegrated in stimulated gastric fluid. But the first units which disintegrates and produces the minimum effective concentration when the study was continued in phosphate buffer pH 6.8 and further the second units which is prepared by controlled release polymer disintegrated and produce a controlled release drug to maintain the peak plasma concentration. In conclusion the matrix pellets were an alternative approach to reservoir type pellets for extended delivery of drugs.***

Keywords: ***Esomeprazole magnesium trihydrate, Matrix pellets, Controlled release polymers, Extrusion Spheronization, Enteric coated pellets.***

I. INTRODUCTION

The oral route of drug administration is the most user friendly means of drug administration having the highest degree of patient compliance. Pharmaceutical pellets are versatile carrier for sustained release and delayed release oral formulations that release the medicament in the gastrointestinal tract for a prolong period of time. Pellets can be defined as small free flowing spherical units normally the size various from 0.5mm to 1.5mm; intended for oral administration manufactured by the agglomerate of fine powders or granules of bulk drugs and excipients using appropriate processing equipments. Pellets are used successfully as an alternative to conventional tablets shows maximum drug absorption and reduced peak plasma fluctuation. Multiple Unit Pellets (MUPS) comprises numbers of discrete particles that are combined into one dosage forms.

Peptic Ulceration is one of the common disease affecting millions of people. It is now considered to be one of modern age epidemic affecting nearly 10% of world population. Esomeprazole Magnesium Trihydrate is the S- isomer of Omeprazole leading to greater inhibition of gastric acid secretion compared to Omeprazole, the first Proton Pump inhibition (PPI) to be developed as a single isomer for the use in the treatment of the acid related diseases. The drug is also used to treat symptoms of Gastro Esophageal Reflux Disease (GERD). The disease is characterized by backward flow of stomach acid (gastric reflux) into esophagus. It results in heart burn, mucosal damage and chronic injury to esophagus.

Beside GERD, Esomeprazole is also recommended to treat Peptic Ulcer caused by NSAIDS and H.pylori infection. The drug reduced formation of excessive stomach acid by inhibiting H+/K+ ATPase in to Parietal cells of the stomach. This results in prevention of further damage and allows healing of damage oesophagus. Esomeprazole belongs to the class as Sulfinyl benzimidazoles has molecular formula C17 H19 N3 O3 S and the molecular weight 461 da, melting point is 155^0C. The recommended dose of Esomeprazole for Peptic

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Ulcer, GERD and reflux esophagitis various from 20 to 40 mg per day for a period of 4 to 8 weeks. As per pharmacokinetic data Esomeprazole is rapidly absorbed and shows bioavailability about 55% after oral administration and its peak plasma concentrations of 0.5 – 1.0 mg/1 is achieved within 1-4 hours. The majority of the drug bound to Plasma Proteins, and metabolized by the hepatic system. The drug is eliminated mainly in the urine as metabolite (about 80) and the remaining 20% as feces. The average medium half life of Esomeprazole is 1 to 1.5 hours. Pelletization is defined as an agglomeration process for converting fine powders/granules of bulk drugs / exicipients in to small free flowing, spherical or semispherical units referred to as Pellets

Up to now, no or few controlled/sustained release Multiple Unit Pellets of Esomeprazole has been developed. Due to the rapid degradation that occurs in acidic gastric fluids enteric coating is required. Taking all the above into account this study concerns with design and evaluation of controlled release multiple unit pellets was prepared by Extrusion and Spheronization technology using Hypromellose and Xanthan gum as controlled release polymers.

II. MATERIALS AND METHODS

MATERIALS

Esomeprazole Magnesium Trihydrate was obtained from Mylan Lab.Ltd, Hydroxy Propyl Methyl Cellulose and Xanthan gum were kindly given by Triveni Chemicals, Manitol, Polyvinyl Pyrolidone (PVPK30), Talc, Magnesium Sterate and other excipients and chemicals used were of analytical grade.

Pre formulation studies were carried out for appropriate selection of excipients in view of Eomeprazole magnesium trihydrate modified release pellets.

ANGLE OF REPOSE

Angle of repose is used to determine the flow properties of powders, pellets (or) granules. The accurately weighed powder / pellets were taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the Powder blend / pellets the powder blend / pellets was allowed to flow through the final freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$\tan\theta = h/r$

where h and r are the height and radius of the powder cone.

BULK DENSITY

Bulk density of the pellets was determined by pouring pellets into a graduated cylinder via a large funnel and measuring the volume and weight

Bulk density = weight of granules / bulk volume of granules

TAPPED DENSITY

Tapped density was determined by placing a graduated cylinder containing a known mass of granules and mechanical tapper apparatus, which was operated for a fixed number of taps until the Powder bed volume has reached a minimum volume. Using the weight of the drug in the cylinder and this minimum volume the tapped density maybe computed. Tab density = weight of granules / tapped volume of granules

CARR'S INDEX

Carr's index is measured using the values of bulk density and tapped density. The following equation is used to find the carr's index.

Carr's index = (TD – BD)/TD X 100

where

TD = Tapped density

BD = bulk density

HAUSNER'S RATIO

Hausner's ratio is a number that is correlated to the following flowability of a powder (or) granular material. The ratio of tapped density to bulk density of the powders is called the Hausners ratio.

It is calculated by the following equation

Hausner's ratio (H) = TD / BD

where

TD = Tapped density

BD = bulk density

Parameters	F1	F2	F3	F4	F5	F6
Angle of repose (°)	22.01±0.54	26.07±0.37	27.57±0.42	25.24±0.52	28.11±0.91	25.12±0.51
Bulk density (g/cm3)	0.457±0.008	0.56±0.04	0.455±0.005	0.54±0.05	0.44±0.006	0.48±0.09
Tapped density (g/cm3)	0.543±0.002	0.58±0.06	0.536±0.006	0.504±0.005	0.508±0.007	0.501±0.006
Compressibility index(%)	11.53±0143	16.41±0.352	12.91±0.147	11.51±0.129	12.87±0.126	11.81±0.147
Hausner's ratio	1.118±0.002	1.213±0.006	1.149±0.017	1.128±0.002	1.147±0.004	1.135±0.002

Table 1: Preformulation parameters of powder blend

FOURIER-TRANSFORM INFRARED SPECTROSCOPY (FTIR): Sample about 5 mg was mixed thoroughly with 100 mg Potassium bromide IR powder and compacted under vacuum at a pressure of about 12 psi for 3 minutes. The resultant disc was mounted in holder in IR spectrophotometer and the IR spectrum was recorded from 4000 cm -1 to 625cm-1 in a scan time of 12 minutes. The resultant spectrum were compared for any spectral changes.

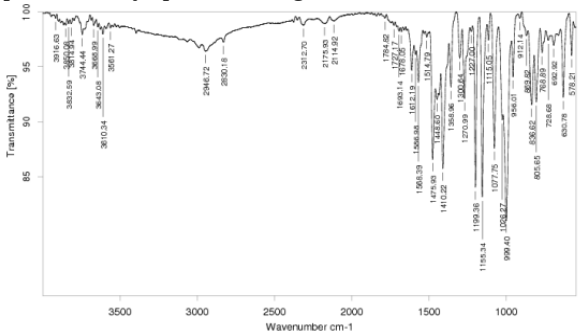


Figure 1: FT-IR Spectrum of Esomeprazole pure drug

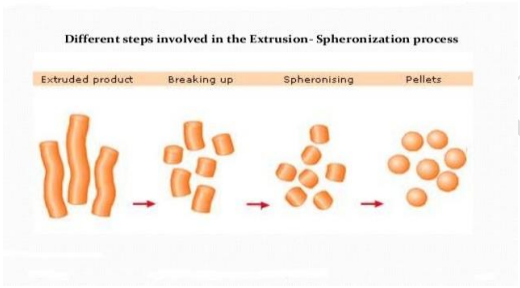
III. FORMULATION OF ESOMEPRAZOLE PELLETS

EXTRUSION-SPHERONIZATION

- ✓ The Extrusion-Spheronization technique is the most popular method of producing pellets.
- ✓ The process involved 4 steps
  - Preparation of wet mass (granulation).
  - Shaping the weight loss into cylinder (extrusion).
  - Breaking up the extrudates and rounding the particles into sphers (Spheronization)
  - And drying of the pellets.
- ✓ Wetting operation brings the material to a state in which porosity is linked to water content
- ✓ Spheronization is only shaping process which maintain hedro-textural state

Figure 2: EXTRUDER

Figure 3: SPHERONIZER



ADVANTAGES

- ✓ Ability to incorporate higher levels of active components without producing excessive larger particles.
- ✓ Two (or) more active agents can be easily combined in any ratio in the same unit.
- ✓ Particles having higher bulk density, low hygroscopicity, dust free narrow particle size distribution and smoother surface can be produced.

FORMULATION DEVELOPMENT

Required quantity of Eomeprazole magnesium trihydrate, Controlled release polymers Hypromellose (HPMC), Xanthan gum diluents Mannitol, Microcrystalline cellulose, polyvinyl pyrrolidone and talc are mixed and prepared a wet mass (granulation). The wet mass was introduced in extruder, shaping the wet mass in to cylinder. Using the spheronizer the formed cylinder extrudate was breaked and rounding the particles in to spheres. (spheronization) and finally the pellets were dried. For different release of multiple unit pellet three different concentration of controlled release polymer were used, the formulated Eomeprazole magnesium triihydrate were packed in hard gelatin capsules were enteric coated with enteric polymer. Among the two controlled polymers HPMC (1:1) possess good quality controlled release profile.

IV. EVALUATION OF PELLETS

CALLIBRATION OF ESOMEPRAZOLE

A drug content equal to 40 mg of esomeprazole magnesium trihydrate was weighted and transferred into a 100 ml volumetric flask. To this 10 ml of ethanol was added and shaken for 15 min. This was made up to the mark with pH 6.8 phosphate buffer. This was filtered using a whatmann filter paper. 10 ml of the filtrate was transferred into 100 ml volumetric flask and made up to the mark with pH 6.8 phosphate buffer and assayed at 301 nm using UV spectrophotometer.

IN VITRO DISSOLUTION TESTS

Dissolution rate was studied by using digital six stage dissolution test apparatus USP PaddleII model, (tap machines Mumbai) using 900 ml .of 0.1 N HCl for 2 hrs. and 900 ml phosphate buffer for 10 hours as dissolution medium and the temperature of the dissolution medium was maintained at 37±0.5°C. Aliquots of dissolution medium were withdrawn first 2 hrs. in a acidic medium, followed by pH 6.8 phosphate buffer for further 12 hrs.

1 ml of sample was withdrawn after every hour and was replaced by an equal volume of fresh dissolution medium of same pH. Collected samples were analysis spectrophotometer at 301 nm.

ACCELERATED STABILITY STUDY OF THE OPTIMIZED BATCH

Stability study is used to predict the shelf life of the product by accelerating the rate of decomposition, preferably by increasing the temperature of reaction condition. The pellets were packed in aluminum pouch and charged for accelerated stability study at 40̊ C and 75% RH for 3 months in accelerated stability chamber. At the end of the study the optimized formation was evaluated for drug content and *in vitro* release profile.

V. RESULTS AND DISCUSSION

COMPATIBILITY STUDIES

In order to investigate the possible interaction between Esomeprazole and distinct polymers FT - IR studies work carried out. FT - IR results proved that the drug was found to be compatible with excipients as wave numbers are almost similar for pure drug.

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EVALUATION OF PREFORMULATION PARAMETERS

The Esomeprazole powders / pellets were evaluated for angle of repose, bulk density, tapped density, carr's index and Hausner's ratio. From the results of micrometrics studies drug shows good flow property and compressibility property.

IN VITRO DISSOLUTION STUDIES

In vitro dissolution studies for first 2 hours in acidic medium had revealed the acid resistance capacity of capsule containing pellets. The dissolution behavior of pellets in phosphate pH6.8 shows Optimized batch found to satisfactory dissolution profile.

SCANNING ELECTRON MICROSCOPY

Microscopy figures of Optimized formulation that pellets appeared to exist as spherical discrete units while the surface morphology of the pellets was compact, continuous and is porous in nature SEM demonstrated the spherical nature of the pellets.

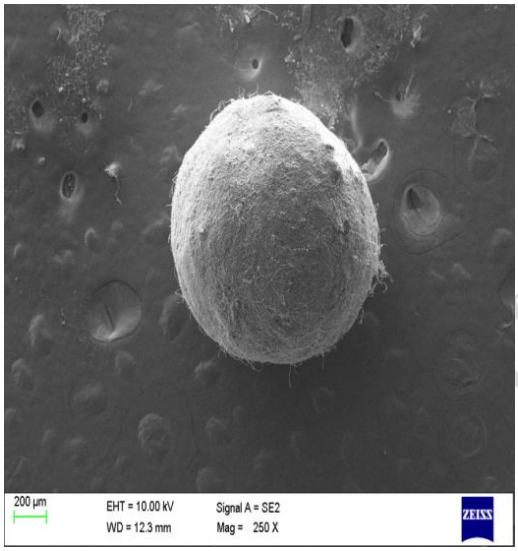

Figure 4: SEM Study of Esomeprazole pellet

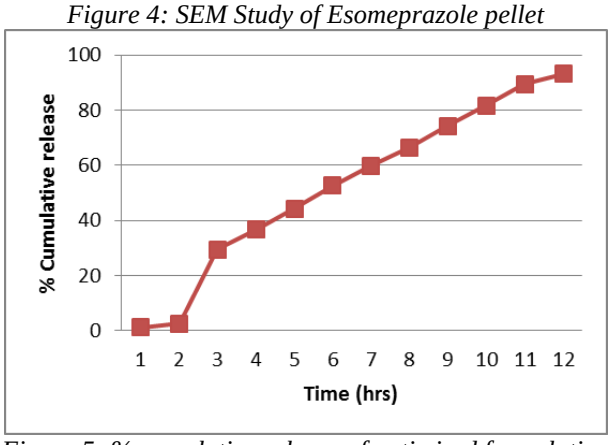

Figure 5: % cumulative release of optimized formulation

STABILITY STUDIES

No significant difference was found between the drug release profiles of the stored samples after three months. There were no signs of visually distinguishable changes in appearance and color of the pellets. The drug content was comparable with that of the control samples and within limits (±10%). From the result of above it can be concluded that the formulation had enough stability under accelerated stability test conditions for three months.

VI. CONCLUSION

From the above research finding it can be concluded that an enteric coated Esomeprazole Magnesium trihydrate Multiple Unit Pellets could be developed by using Hypro mellose 1:1 (drug: polymer) as Controlled release polymers using Extrusion and Spheronization techniques to deliver the acid unstable drug safely in duodenum to achieve better bioavailability.

REFERENCES

[1] Goodman and Gilman: The Pharmacological Basis of Therapeutics, 10th edition, 2003, 1007-1008.
[2] www.drugs.com/monograph/Esomeprazole magnesium dehydrate.
[3] Chein Y W, Novel drug delivery systems, 2nd edition, Marcel Dekker, NewYork, 2000,43-135.
[4] Leon Lachman, Herbert A.Liberman and Joseph L.Kanig. The Theory and Practice of Industrial Pharmacy, 3rd Edition, Bombay: Varghese. 331-332, 364-368.
[5] AnselCH and PoppovichNG Pharmaceutical Dosage Forms and Drug Delivery Systems,6th edition New Delhi B.I Waverly Pvt Ltd,l1995,213
[6] Aulton.ME Pharmaceutics: Science and Dosage form Design. 2nd ednChurchil Livingstone USA 2002,213-227 & 204-206.
[7] Leon Lachman, Herbert Liberman and Joseph L.Kanig. The Theory and Practice of Industrial Pharmacy, 3rd edn Bombay: Varghese: 293-329.
[8] International Conference on Harmonisation (ICH) harmonized tripartite guideline for stability testing of new drugs substances and products Q1A (R2) Aug-2003. Q1A (R2) Mar 2004.
[9] Nagarjunanaik.R, Laksmano Rao potti, Rama Kotaiahmogali, Prasad Rao M, Siva sankar.R "Formulation and evaluation of Esomeprazole magnesium dihydrate multiple unit particulate system (pellets). As a delayed Release dosage Form", Int.J. Res. Dev. Pharm. L.Sci. Vol.3, No.2, PP 935-942.
[10] Jagadeesh Kumar Ega,"Formulation and Evaluation of Esomeprazole Magnesium delayed release Tablets 40mg", I nt. J.Res & Application 2(6): PP 242-252.
[11] NS Dey, S Majumdar and MEB Rao," Multiparticulate Drug Delivery systems for controlled release, Trop J pharm Res, Sep 2008; (7(3) PP1067-1075.
[12] Kammela K Chakravarthy, MohammadyounusShahidulla Shaik, Sai venkatavedavyaspisipati," Formulation and Evaluation of Enteric coated pellets of Omeprazole", Int.J.Drug Dev 2 Research 2012 vol.4 pp 257-264.
[13] A. Badoni, G. Gnanarajan, P. Kothiyal,"A Research

Article on Formulation and Evaluation of Enteric coated loaded with Rabeprazole for mucoadhesive Drug Delivery, the Pharma journal.com vol 1 no.8, 2012, pp 50-56.

[14] Sagar Muley, Tanaji Nandgude, Sushilkumar Poddar," Extrusion - Spheronization a promising pelletization technique-In–depth review, Asian Journal of Pharmaceutical Science II (2016) pp 684-699

[15] Y. Surekha, P. Venugopalaiah, K. Gnan Prakash and M.Gobinath," Design and Characterization of Enteric coated Delayed Release Pellets of Rabeprazole Sodium, ajadd.co.UK,[1] [4] [2013] pp 422-434.