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Fabrication and Evaluation of Oral Multi-Particulate Tablets of Proton Pump Inhibitors: Esomeprazole as a Model

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ABSTRACT

Esomeprazole, a proton pump inhibitor, inhibits gastric acid secretion and used to treat many acid-related gastric/duodenal diseases in adults and children. The present article investigated the development of an oral delayed-release multi-particulate tablet of Esomeprazole, which consists of enteric coated pellets of esomeprazole. Such dosage form offers the healthcare providers a higher dosage flexibility to give the appropriate dose regarding the patient age and the disease state of the patient. In addition, the proposed dosage form enhances the physicochemical stability of coated drug by forming multi-unite pellets system (MUPS) ®. Compression of coated pellets is an arduous process and requires the optimization of several formulations and processing variables; among it includes size, nature, and amount of tableting additives as well as the applied compression force. In this study, several trials were executed to prepare a satisfactory product by using the direct compression method with different directly compressible fillers, having suitable cushioning properties, like spray dried lactose, microcrystalline cellulose (MCC), and dibasic calcium phosphate. In this study, it was found that adding up to 49% of (MCC) offered greater protection to the coated pellets, and greatly maintained the integrity of the multi-particulate tablet—even under a compression force of about 3 tons. This research work led to successful formulation of esomeprazole delayed release multi-particulate tablets containing enteric coated pellets equivalent to 20 mg of esomeprazole magnesium trihydrate using the direct compression method.

Keywords: Esomeprazole (MUPS®), Multi-Particulate Tablet, PPIs.

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INTRODUCTION

The oral route is the most commonly used for administration of pharmaceutical preparations, and tablets of different kinds are the most popular dosage forms available in the market preferred by the physicians and patients. [1] Proton pump inhibitors (PPIs) are by far the most active blockers of gastric acid secretion and are commonly used for treatment of gastro-duodenal acid-related disorders even in specific populations such as pregnant women. [2,3] Proton pump inhibitors characterized by similar core structure and mode of action but differs in substituent groups accordingly differs in therapeutic potency and in their physicochemical properties and consequently their stability in different media. [4]

Esomeprazole magnesium trihydrate is a substituted benzimidazole, the S-isomer of omeprazole, blocks the gastric parietal H^+/K ATPase permanently. Thus, reduce gastric acidity, so widely used to treat erosive esophagitis, gastro-esophageal reflux disease (GERD), acid associated dyspepsia and as an adjuvant in the eradication therapy of *H. Pylori* infection where majority of duodenal and peptic ulcers are related to this bacterium. [5] The stability of PPIs is dramatically affected by the pH. PPIs are less stable and rapidly degrade in acidic condition but has adequate stability in alkaline condition. So, an enteric coating is essential step during dosage formulation of these drug materials into oral dosage forms, in order to prevent drug degradation in the acidic media of the stomach. The enteric coating technique can be applied to the whole dosage as single unit like enteric coating tablet or applied individually on minute, free flowing, spherical or semispherical particulate like enteric coated pellets. Both forms are designed to release active ingredients after programmed time period following administration depending on pH of the gastro intestinal tract as the enteric coating dissolve in the alkaline condition (pH 6.8) of the small intestine and release the active constituent for absorption at the same time maintain it from degradation in the gastric acid condition. [6]

Pellets can be defined as agglomerates of fine powder mixture consist of active drugs and inert excipients. They are produced by pelletization techniques which are a size enlargement method or agglomeration process that result in formulation of minute, free flowing spherical or semispherical solid particulate with size ranged between 0.5-1.5 mm intended for oral administration. [7,8] Pellets are of a great interest in manufacturing of pharmaceutical product for varying medicinal substances for many purposes like:

- They offer flexibility in the design and development of the dosage form.
- Ensure the safety and efficacy of the bioactive agent.
- Improve the chemical stability and physical characteristics.
- Enhance the bioavailability for gastric-sensitive drug or minimize the side effect for gastric-irritant medicate thus enhancing patient acceptance [9]

Production of pellets for pharmaceutical purposes can provide different drug delivery properties primarily for controlled-release, delayed-release, sustained-release, or targeted-release or pulsatile release. To achieve the desired release profiles, they can be modified by many ways based on the type and amount of polymers coating materials or by formulating matrix pellets to obtain the desired formula release pattern. [7] The final dosage form for the coated pellets may be either filled in a bottle or compressed into tablets. Compaction of the multiple unite

pellets commonly called MUPS which is more recent and challenging technologies that offer several advantages over their single-unit dosage counterparts, as they combine the benefits of both tablets and pellets-filled capsule in one dosage form with improved physic-chemical stability compared to suspension. Therefore, compacted multi-particulate tablets is the preferred final dosage form for coated particles, but requires relatively complex manufacturing processes/formulation variables. [10] One challenge for producing multi-particulate tablets is that the polymer coating might not withstand compressive force during compaction and might not sustain compression modified drug release characteristics as a consequence of deformation of the enteric coated film and consequently altering drug release pattern. [11] The selection of optimal excipient is essential to protect the coating film from such changes at tableting of pellets. Excipients that possess cushioning action and plasticity feature such as polyethylene glycol (PEG) and microcrystalline cellulose provide the best protective effect and can be used as filler. [12] These parameters in addition to another factor related to pellets characteristic and processing procedure especially compaction pressure should be considered during manufacturing of multi-unit pellets drug delivery system. [13]

The aim of this research work is to develop oral multi-particulate tablets consist of esomeprazole 20 mg in form of enteric coated pellets by direct compression method. Our method utilized an appropriate tableting excipient which is essential to prevent any damage to the polymer coat surface or rupture of the pellets itself with adjustment of the compression force during compaction of the pellets and filler powder mixture. To achieve this protocol, series of formulation using different fillers with constant amount of esomeprazole pellets will be developed, and various parameters of quality control study concerning hardness, friability, pellet intact observation and dissolution pattern are to be evaluated.

MATERIALS AND METHODS

Materials

Esomeprazole magnesium trihydrate as pure powder and enteric coated pellets supplied by (Disto pharmaceutical PVT. LTD. India), spry dried lactose supplied by (SDI, Iraq), microcrystalline cellulose (Avicel PH 102, PH 101) and dibasic calcium phosphate supplied by (College of Pharmacy, University of Baghdad).

METHODS

Various formulas of modified release tablets of esomeprazole multi-particulate were prepared utilizing direct compression technology by mixing required quantity of enteric coated esomeprazole pellets with varying types of tableting excipient (filler) uniformly in a mortar and the whole blend was mixed gently and thoroughly for five minutes by the pestle before magnesium stearate was added and mixed for additional two minutes.

Then, the resulting blend was loaded manually into the compression die machine and compressed into the multi-particulate tablet using flat face punch with diameter of 10 mm. under different compaction pressure to find the most satisfactory one. [14] The composition of various formulations of multi-particulate esomeprazole dosages forms are shown in the table (1)

Key formulation variables in tableting of a coated pellet of esomeprazole

Different variables play essential role in manufacturing multi-particulate system in regard to maintaining the integrity of pellets or coating film, compression of such pellets is a challenging task because the polymers form coating might not withstand compressive force during compaction triggering fissuring in the coat or fracturing of the whole pellets themselves. Hence, multiparticulate dosage form processing requires optimizing several key formulation variables like nature, size and amount of tableting excipients. [11] Moreover, the effect of compaction processes because excessive pressure can lead to deformation of the enteric / film coating and hence to distorted drug release or damage of sensitive drugs. Furthermore, adjusting the physical properties of the pellets such as the size, shape, density, porosity, and the type and amount of polymer coating play a significant role in facilitating the compaction of coated multi-particulates into tablets with little defect or damage to coating polymer/the pellets themselves. [15,16]

Tableting Excipients

The required filler used for tableting of pellets should prevent the direct contact of the pellets and protect the coating surface by filling in the void spaces between them and act as cushion throughout compression. In general, excipient materials like PEG and microcrystalline cellulose that deform plastically give the greatest protecting effect. [17] This type of tableting excipients usually yield a sufficiently hard tablets at low compression force that can endure the handling of the product with little effect. In addition, the filler should have a particle size matching the pellets' size to yield uniform mixture with the coated particles, avoiding segregation. Consequently, avoiding weight variation and poor drug content of the produced tablet. [18]

Compression force for tableting esomeprazole coated pellets

One challenge in tableting of enteric coated pellets is maintaining the desired drug release after compaction. It has been reported that polymer coated multi-particulates could be compacted into tablets either alone or with a blend of appropriate excipients that have Cushing properties. Coating polymer must have sufficient plasticity and flexibility to withstand the changes in shape and deformation during tableting, as a result the force of compaction in tableting machine. Furthermore, to maintain the integrity of the pellets as complete unite in combination with tableting excipient and produce oral multi-particulate tablets. [19]

Evaluation of compressed multi-particulate esomeprazole tablets

The generated formulas were assessed by the tests mentioned below:

I-Hardness: the hardness of five tablets from each formula was assessed separately by means of Monsanto hardness tester.

II- Friability test: Roche friabilator was used for measuring the friability of the compressed multi-particulate tablets which calculated as a percent of weight loss of 10 tablets from each formula after 100 revolutions.

III- Drug content assay: random samples of 5 compressed tablets from each prepared formula were crushed into powder in a mortar and weight equivalent to 20 mg of esomeprazole magnesium trihydrate was taken into a volumetric flask containing phosphate buffer pH 6.8 as

solvent. Esomeprazole was dissolved using ultrasound with continuous shaking for 10 min using to ensure complete dissolution. The amount of esomeprazole was measured by using UV-spectrophotometer absorption at the wavelength of maximum absorbance of 303 nm. [20]

VI- Dissolution study: dissolution test was performed on three tablets from each prepared formula using USP dissolution apparatus type 1 (basket method) with dissolution medium composed of 900 ml 0.1 N HCl (pH 1.2) for first two hours subsequently in 900 ml phosphate buffer (pH 6.8) for the rest of experiment at 37°C and rotation speed 50 rpm. After that at specific time intervals samples of 5 ml were withdrawn, diluted and examined s by using UV-spectrophotometer at the wavelength of maximum absorbance 303nm for esomeprazole. [21]

RESULT AND DISCUSSION

Variables affecting the fabrication of esomeprazole multi-unite pellets matrix tablet

The esomeprazole magnesium trihydrate pellets are usually coated with the cellulosic/acrylic polymer. In manufacturing of a tablet containing pellets by direct compression technology an ideal matrix formulation should contain appropriate filler with an acceptable mechanical property and resistant to compaction at the smallest amount possible. The filler maintains the integrity of both the pellet core and polymer coating surface during compaction and get more elegant tablets' dosage form with acceptable physical characteristics like hardness, friability, surface condition as well as required drug release pattern. [22] All the prepared multi-particulate tablets contain 50% of coated pellets which is equivalent to 20 mg of esomeprazole magnesium trihydrate as usual adult dose, the rest of dosage weight represents tableting excipients. Addition of 30%–60% of tableting excipient is necessary to fill the void space between densely packed pellets and avoid any damage to the polymer coat and maintain its functional property without or with minimum destruction to the coated pellets forming the multi-particulate system. Although several researches had used different percent of drug loaded pellets ranging from 10% to 90% in manufacturing multi-particulate tablet, it was found that pellet percent below 60% showed acceptable findings. [23] Therefore, in this research work pellets composed 50% of the tablet weight to ensure maximum protection of the enteric coated pellets by tableting excipient at suitable compression force

Influence of excipient type

Multi-particulate tablets containing 50% pellets and 50% excipients were prepared by direct compression process. Different types of directly compressible fillers were used to assess the compaction process and to prevent the damage and rupture of the coated pellets, the fillers that used was lactose, dibasic calcium phosphate and microcrystalline cellulose. The ideal filler substances should prevent the direct contact between the coated pellets and act as cushioning agent to ensure that the function of polymer coat remains intact upon compaction. [24] . It was found that MCC has the best protective action for esomeprazole pellets to be compacted into tablets, this effect is attributed to the physical properties of MCC particles which have good compaction characteristic and consolidated by plastic deformation so it is better than other diluents for protection of coated particles, [25] the same outcomes were observed by Habib et. al. which found that high level of MCC revealed lower yield values and thus more compressible than those with high lactose levels. [26] It was also found that the inclusion of approximately 50 percent of excipients with pellets in tablet formulation is appropriate, since this proportion allowed the coated particles to be freely embedded in the matrix without segregation and the filler fill the void spaces between them during compression into multi-particulate tablets, the same findings were reported by Yogesh C. Patheon and Sateesh Sathigari in manufacturing tablets of coated multiparticulates. [27]

Compression force

The suggested formulas were compressed with different compression force (2, 3 and 4 ton) to study the effect of compaction pressure on the integrity of coated pellets and at the same time produce multi-particulate tablets with physical properties like hardness and friability which is able to withstand shopping and handling by the patients as oral dosage forms. It was noted that at low compression force (2 tons) yield chipping and friable tablet while at higher pressure (4 tons) cause destruction of the pellets inside the matrix tablets especially for those which contain DCP as diluent. As a result, any formulas prepared under this compaction pressure it will be excluded if a formula failed to produce satisfactory multi-particulate. The remaining formulas produced by compression force equal to three tons showed acceptable multi-particulate tablets in regard to physical characteristics and pellets integrity so they can be adopted in this research work.

Evaluation of compressed esomeprazole multi-particulate tablets

As shown in the table (2), the hardness of esomeprazole multi-particulate tablets was close values among formulas, and this outcome may be attributed to the type of filler used as matrix for tableting of coated pellets. Mean tablet hardness following the order MCC (Formula MS-8) > Lactose (Formula MS-2) > DCP (Formula MS-5). Depending on the physicochemical properties of tableting excipient as lactose is water soluble filler and dibasic calcium phosphate is water insoluble and non-swellable filler while microcrystalline cellulose is water insoluble and swellable filler the same values of tablet hardness containing different excipients were observed by Radoslaw Kraciuk. [28] It is well known that the high hardness, for formula using MCC as diluent, is due to MCC's ability to deform in predominantly plastic manner, which is believed to be an important factor affecting the compressibility of MCC and formation of hard tablet at a low compression force [29] as shown in formula MS-8. Similar finding was observed by Bendgude et.al. when examined the effect of different types of excipients on physical properties of compressed HPMC matrix tablets. [30]. Friability is another measured test of tablet's strength, as follows in table (2). The formulas MS-2 and MS-8 using lactose and MCC as tablet matrix showed acceptable weight loss which is less than 1% of their weight. The higher value of friability noted for formula MS-5, which contain DCP as filler, could be attributed of DCP based matrix formulation to compact into a multi-articulate tablet with sufficient integrity at low compression force. Therefore, this formula will be excluded from this study because of it failed to pass the post-compression physical parameters for oral tablets. The higher value of friability suggests that the tablet cannot withstand the rigors of production, transportation or handling. Other formulas have shown low friability values arisen from presence of considerable amount (50% w/w of tablet weight) of filler

of a good plasticity and compressibility characteristics which improve physical parameters of tablets (hardness and friability) and enhance skeleton integrity. [31]

Drug uniformity test, the drug content values showed in table (2) for the prepared multi-particulate tablets indicated that all the prepared formulas complied with United States Pharmacopeia specification which is 90-110% of esomeprazole content in each individual tablet. [32]

In-vitro dissolution study of enteric coated esomeprazole pellets compressed into a tablet utilizing inert excipients (lactose and MCC) was performed and the release pattern is shown in figure (1) and (2). It can be seen that formula MS-8 which contain MCC as filler exhibit acceptable delayed dissolution data with approximately 5% of drug being lost in 0.1N HCL solution through 2 hours, after that exposure to the basic medium (phosphate buffer pH 6.8) about 90% of esomeprazole being released within 50 min. so satisfy the USP specifications for delayed release (enteric coated) dosage form which state that "no individual value of drug release profile should exceed 10% when dissolved in acidic phase after 2 hours of operation and not below than 75% of drug content should be released in basic buffer medium after continuous operation in the apparatus for 45 minutes" . [33]

A similar situation was discussed in a study of omeprazole release from enteric coated formulation by Bozdag et.al. [34] This may point that the enteric coated pellets could maintain their coating integrity with little deformation at compaction into tablets. While formula MS-2 consists of lactose as tableting excipient showed more than 10% of drug release after 2 hours of operation and fast drug release at short time could indicate that exposing the coated particles to deformation during compaction into a multi-particulate tablet.

Finally, formula MS-8 which contains a blend of enteric coated pellets and MCC as tableting excipient was showed solid dosage form with suitable physical characteristics in regard to hardness and friability and maintain their skeletal moiety in addition to provide acceptable delayed release profile for drug substances thus can help in improving the treatment efficiency and enhancing patient compliance. So, it will be selected as the best formula for fabrication of multi-particulate tablets for proton pump inhibitor (esomeprazole magnesium trihydrate).

CONCLUSION

The trials investigated in this research work led to successful formulation of esomeprazole delayed release multi-particulate tablets containing enteric coated pellets equivalent to 20 mg of esomeprazole magnesium trihydrate using the direct compression method. This process is, usually, a challenging task which needs optimization of several key variables include formulation materials (tabletting excipient), process parameters (compression force) as well as the pellets to excipients ratio. Based on the results obtained, we can conclude that a ratio at least 50% of tableting excipients must be used with 50% of coated pellets to protect the units and produce intact tablet with sufficient mechanical properties. MCC can be selected as the best directly compressible filler due to its plasticity and cushioning action so prevent damaging the polymer coat film and maintaining the pellets integrity beside can form hard tablets at low compression force about 3 tons.

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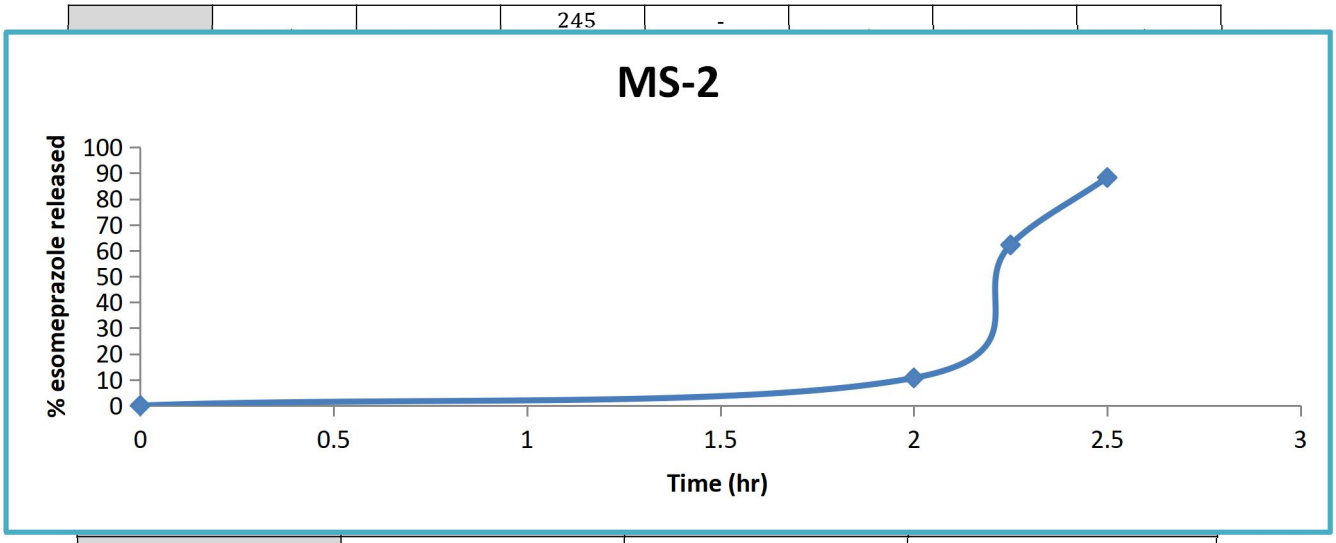
Table 1: Different Formulas of Esomeprazole Multi-Particulate Tablets*

Formulas	Esomeprazole pellets	Spry dried lactose	Dibasic calcium phosphate	MCC blend	Magnesium stearate	Compression force (ton)	Total weight
MS-1	250	245	-	-	5	2	500
MS-2	250	245	-	-	5	3	500
MS-3	250	245	-	-	5	4	500
MS-4	250	-	245	-	5	2	500
MS-5	250	-	245	-	5	3	500

			245	-			



MS-2	4.5	0.77	96.8
MS-5	3.6	1.08	92.7
MS-8	5.3	0.39	99.3

(*) All the amount in the table is in (mg) weight.

Table 2: physical properties of the different formulas of the manufactured Esomeprazole Multi-Particulate tablets produced by the direct compression method.

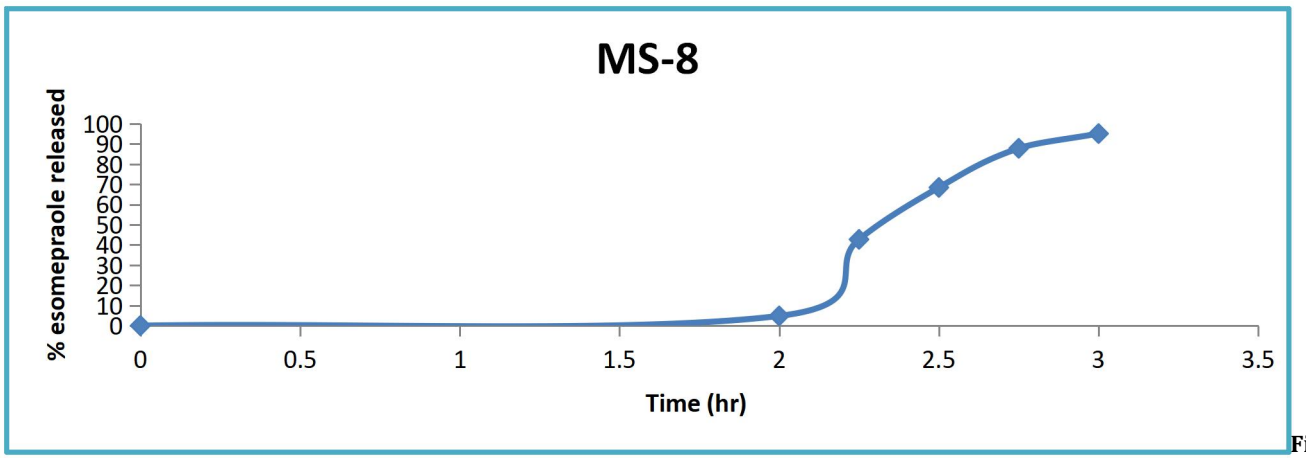


Figure 1: The cumulative release profile, in buffer medium, at 37 ˚C, of the formula number eight (MS-8), MCC-based formula, of the Esomeprazole Multi-Particulate tablets produced by the direct compression method.

Figure 2: The cumulative release profile of Esomeprazole from lactose based multi-particulate tablets in buffer medium at 37 ˚C