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Original Article

FORMULATION AND EVALUATION OF BILAYER MATRIX TABLETS OF AMOXICILLIN AND ESOMEPRAZOLE AS AN ORAL MODIFIED RELEASE DOSAGE FORM FOR TREATMENT OF PEPTIC ULCER

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ABSTRACT

Objective: The objective of the present study is to formulate a dual therapy of peptic ulcer containing antimicrobial agent amoxicillin and anti-secretory agent esomeprazole, utilizing the concept of bilayer tablet system for the effective treatment of *H. pylori* associated gastric/duodenal ulcer, in an attempt to improve bioavailability and to get maximum therapeutic benefits and patient compliance about the treatment.

Methods: Different formulas of 500 mg amoxicillin were prepared as sustained release layer by wet granulation method; similarly, different formulas of 20 mg esomeprazole in form of enteric coated pellets was prepared as extended release matrix layer by direct compression technique, using pH-independed hydrophilic Eudragit polymers (E-RL100 and E-RSPM type) as matrix forming agent. The physical characteristics and release properties for compressed amoxicillin and esomeprazole matrix tablets were studied in addition the effect of polymer type, polymer concentration, polymer combination and ratio, effect of diluent type, binder type and method of preparation on the release of amoxicillin and esomeprazole from compressed matrix tablets.

Results: The results showed that formulas prepared with Hydroxypropylmethyl cellulose (HPMC K100M) and Xg in a ratio of 4:1 and PVP as binder was capable to retard the release of amoxicillin for 12 hours which according to dosing frequency of amoxicillin in treatment of peptic ulcer (twice daily) it will prevent drug free interval so achieve complete eradication of *H. pylori*, thus it was selected for preparation of bilayer tablet. Regarding esomeprazole, formula ES-5 (which consist of 20% w/w E-RS + 7.5% w/w ethyl cellulose EC) was the best formula since it showed higher (f_2) comparing to reference release for enteric dosage form of esomeprazole among other formulas, so it will selected for bilayer tablet formulation with optimized formula of amoxicillin layer. Kinetic modeling of the release data for the selected formula (AM-12, ES-5) showed that the mechanism of drug release pattern follows anomalous or non-fickian diffusion. The prepared bilayer tablets were further subjected to evaluation of their physical properties and in vitro release behavior.

Conclusion: In the light of the results obtained from this research it can be concluded that amoxicillin can be prepared as a sustained release tablets using HPMC K100 and Xg. as matrix forming polymers in a polymer-polymer ratio of 4:1, respectively. Also, esomeprazole can be prepared as extended release multi particulate tablets using pH-independed hydrophilic Eudragit polymers (E-RSPM type) as matrix forming agent with EC.

Keywords: Amoxicillin, Esomeprazole, Bilayer tablet, Peptic ulcer.

INTRODUCTION

The oral route remains the most considered one for administration of drugs and tablets of various types still the ruling dosage form since years [1]. Modified release tablets are coated or uncoated tablet that contain special excipients or they are prepared by special procedures, or both, designed to modify the rate, place or time of release of the active substance(s) [2]. Layered tablets, type of modified release, prepared by compressing several different granulations fed into a die in succession, one on top of another, in layers. Each comes from a separate feed frame with individual weight control to form two-or three-layered tablets, depending on the number of separate fills. Each layer may contain a different medicinal agent with varying release profiles [3], and they are designed for many reasons:

- To control the delivery rate of either single or two different active pharmaceutical ingredients.
- To separate incompatible active pharmaceutical ingredients from each other, to control the release of active pharmaceutical ingredients from one layer by utilizing the functional property of the other layer (such as, osmotic property)
- To modify the total surface area available for active pharmaceutical ingredients layer either by sandwiching with one or two inactive layers in order to achieve swell able /erodible barriers for modified release.
- To administer fixed dose combinations of different active pharmaceutical ingredients, prolong the drug product life cycle, and fabricate novel drug delivery systems such as swelling device, buccal / mucoadhesive delivery systems, and floating tablets for gastro-retentive drug delivery [4].

Ideal drugs candidate for bilayer tablet should have the following characteristics

- Drug produce additive/synergistic effect (Anti asthmatic; salbutamol+ theophylline)
- Drugs having opposite side effects, may reduce the side effect like (omeprazole + NSAIDs. and hydrochlorothiazide + amiloride).
- Incompatible drugs
- Low biological half-life (ideal for modified release bilayer)
- Unstable at intestinal pH (ideal for floating bilayer tablets)
- High first pass metabolism with low biological half-life (ideal for buccoadhesive bilayer) [5].

A peptic ulcer is an open sore on the lining of the stomach or duodenum. Gastric and duodenal ulcers are produced by an imbalance between mucosal defense mechanism and the damaging force particularly gastric acid and pepsin. In addition *H. Pylori* infection is a major factor in the pathogenesis of peptic ulcer. It is present in virtually all patients with duodenal ulcer and in about 70% of those with gastric ulcer. The stomach acid and *H. Pylori*

irritate the lining of the stomach or duodenum and cause an ulcer. Most peptic ulcer heals if gastric acid production is adequately suppressed and *H. Pylori* infection is effectively eradicated to restores normal mucosal resistance. Thus treatment of peptic ulcer requires an antibacterial agent like amoxicillin to act against *H. Pylori* bacteria and a gastric acid suppressing agent like esomeprazole to suppress excess acid secretion [6].

MATERIALS AND METHODS

Materials

Amoxicillin trihydrate supplied by "SDI, Iraq", Esomeprazole powder and enteric coated pellets (DISTO Pharmaceutical PVT. LTD. India), Hydroxypropylmethyl cellulose K100M (Sigma, Germany), Sod. Carboxymethyl cellulose supplied by "SDI, Iraq", Carbapol and Xanthan gum (Himedia Limitide, India), Eudragit-RL and -RS (Sigma Chemical Co., USA), Ethyl cellulose (BDH Chemicals,Ltd, England), Lactose and DCP supplied by "NDI, Iraq", Microcrystalline cellulose (Avicel PH 102, PH 101) (Whatman international England), Polyvinylpyrrolidone (PVP)(Riedel De Haen AG Seelze, Honnover, Germany).

Methods

Preparation of amoxicillin sustained release (SR) layer

The composition of different formulas of amoxicillin matrix tablets is shown in table (1), Formula (AM-1 to AM-12) prepared by utilizing wet granulation process while formula AM-13 fabricated using direct compression process. In wet granulation technique; required quantities of drug, polymer(s) and diluent enough to prepare 50 tablets were weighed and mixed uniformly using mortar and pestle, after sufficient time of dry blending of ingredients in mortar, granulating solutions was added at slow rate in the form of fine droplets. Then kneaded until satisfactory consistency was achieved (ball test) [7]. The wet mass was granulated by passing through sieve no. 10, the granulated mass was air dried at room temperature for 30 min. and then dried in tray drier at 40 ˚C for 30 min., knowing weight of granules were mixed with calculated amount of magnesium stearate and talc powder for 3 min. then compressed using 12 mm. flat face punch tableting machine. While formula 13 was prepared by direct compression in which calculated amount of polymers (HPMC K100M + Xanthan gum) and directly compressible filler (MCC) were taken in a mortar and mixed geometrically. To this required quantity of amoxicillin trihydrate was added and mixed slightly with pestle, the whole mixture was blended thoroughly for 10 min. then magnesium stearate and talc was added and mixed for 3 min. Known weight of the final mixture was compressed into tablets using 12 mm. flat face punch tableting machine [8].

Preparation of esomeprazole multi-particulate matrix tablets

Different formulas of esomeprazole multi-particulate modified release tablets were prepared utilizing direct compression technology by mixing pellets with Weighed quantity of polymers and directly compressible filler uniformly in a mortar for 5 min. then magnesium stearate was added, finally The resulted blend was then manually filled into the die and compressed using flat faced punch with diameter of 12 mm [9]. The composition of different formulas of esomeprazole multi-particulate matrix tablets is shown in table (2).

Variables affecting the formulation of multi-particulate tablets of esomeprazole

Compression of coated pellets into tablets is a challenging task as the polymeric coating may not withstand the compression force during compaction, so fracturing the surface of the polymer or the pellet themselves may occurs. Therefore multi-particulate tablets processing required optimizing several key formulation variables including type and amount of the polymer and; nature, size and amount of tableting excipients [10].

Table 1: Different formulas of amoxicillin tablet as sustained release layer (*)

Formulas	AMT	S.CMC	HPMC K100 M	Carbopol	Xanthan gum	acacia	PVP	Lactose	DCP	MCC ph 102	Mg-stearate	Talc	total weight
AM-1	575	135	-	-	-	45	-	131.5	-	-	9	4.5	900
AM-2	575	180	-	-	-	45	-	86.5	-	-	9	4.5	900
AM-3	575	225	-	-	-	45	-	41.5	-	-	9	4.5	900
AM-4	575	-	135	-	-	45	-	131.5	-	-	9	4.5	900
AM-5	575	-	180	-	-	45	-	86.5	-	-	9	4.5	900
AM-6	575	-	225	-	-	45	-	41.5	-	-	9	4.5	900
AM-7	575	-	180	45	-	45	-	41.5	-	-	9	4.5	900
AM-8	575	-	135	90	-	45	-	41.5	-	-	9	4.5	900
AM-9	575	-	180	-	45	45	-	41.5	-	-	9	4.5	900
AM-10	575	-	135	-	90	45	-	41.5	-	-	9	4.5	900
AM-11	575	-	225	-	-	45	-	-	41.5	-	9	4.5	900
AM-12	575	-	180	-	45	-	45	41.5	-	-	9	4.5	900
AM-13	575	-	180	-	45	-	-	-	-	82	9	9	900

(*) All the amounts in the table are in (mg) weight

Table 2: different formulas of esomeprazole multi-particulate modified release layer

Formulas	ESMT pellets	MCC blend	E-RL	E-RS	EC	Mg-stearate	Total weight
ES-1	261	135	-	-	-	4	400
ES-2	261	55	80	-	-	4	400
ES-3	261	55	-	80	-	4	400
ES-4	261	35	-	80	20	4	400
ES-5	261	25		80	30	4	400

(*) All the amounts in the tablet are in (mg) weight

Nature of polymer

The polymers used in preparation /coating of pellets or as a matrix for coated pellets, plays an important role in drug release after compression. It must have sufficient elastic properties to prevent rupture of coating polymer and plastic properties to accommodate the changes in shape and deformation during tableting [11].

Tableting Excipients

The ideal filler used for the tableting of pellets should protect coated pellets by prevent the direct contact and filling in the spaces between them, and act as a cushion during compression. The excipient should result in hard tablets at low compression forces and should not affect the drug release characteristics for multi-particulate tablets in general

materials that deform plastically such as microcrystalline cellulose and polyethylene glycol, give the best protective effect [12].

Evaluation of compressed amoxicillin and esomeprazole modified release layers

The prepared formulas were subjected to following tests:

Hardness

The hardness of 5 tablets from each of the prepared formulas was measured individually using Monsanto hardness tester**.**

Friability test

The friability test was done for the prepared tablet using Roche friabilitor, the friability was calculated as the percent weight loss, after 100 revolutions of 20 tablets from each formula.

Content uniformity test

5 tablets from each prepared formulas were crushed in a mortar then weight of one tablet were dissolved using 0.1N HCL for amoxicillin and phosphate buffer pH 6.8 for esomeprazole as the solvent respectively. The amount of amoxicillin and esomeprazole was determined by employing UV absorption at the wave length of maximum absorbance which is about 272nm. for amoxicillin and 301nm. for esomeprazole using UV- spectrophotometer.

Dissolution test

The in vitro release study of each formula was conducted in USP dissolution apparatus (basket) in 900 ml 0.1 N HCL (pH1.2) for first 2 hrs. then in 900 ml phosphate buffer (pH 6.8) for the rest of experiment at 37 and 50 rpm. under sink condition. Samples of 5 ml were withdrawn at specific time intervals, then filtered, diluted and analyzed spectrophotometrically at the wave length of maximum absorbance for each drug.

Determination of the Release Kinetics

To study the mechanism of drug release from the selected formula, the release data were fitted to various release kinetic models include zero order, first order and Higuche equations. Furthermore, to characterize the release behavior i.e. to understand the mechanism, Korsmeyer – Peppas model was applied [13].

$$M_t / M\infty = K_{KP} t^n$$

Where M_t and $M\infty$ are cumulative amounts of drug release at time t and infinite time (i.e. fraction of drug release at time t), K_{KP} is the constant incorporating structural and geometrical characteristics of controlled release device; and n is the diffusional exponent indicative of the mechanism of drug release [14].

Bilayer tablets preparation

Optimized formulas of amoxicillin and esomeprazole were selected for formulation of bilayer tablets. As previously reported procedure, granules of amoxicillin layer and physical blend of esomeprazole layer were prepared separately. The amoxicillin granules manually poured into 12 mm die and mild compressed so that a flat surface required for adhesion of the esomeprazole layer was created, over this compressed layer the required quantity of esomeprazole blend was poured, then both layers were subjected to optimum compression to form bilayer matrix tablet [15].

Evaluation of bi-layer tablet

Hardness and Friability

The prepared bilayer tablets were evaluated for hardness (n=5) using Monsanto hardness tester and friability (n=20) using Roche friabilator as per the procedures previously mentioned in the evaluation of compressed amoxicillin and esomeprazole controlled release layers.

Content Uniformity Test

The drugs content were determined by using UV spectrophotometer according to the following procedure [16, 17]. Ten tablets were accurately weighed and average weight of the tablets was determined, the tablets were a ground to a fine powder, and powder equivalent to 500 mg of amoxicillin and 20 mg of esomeprazole were weighed separately, and dissolved in 0.1 N HCL and in phosphate buffer pH 6.8 respectively, the resultant solutions were sonicated for 15 min., filtered, suitably diluted and then analyzed spectrophotometrically at the λ_{max} of 272 nm. for amoxicillin layer and 301 nm. for esomeprazole layer.

Bilayer Tablet's Dissolution Study

The in vitro release study of the prepared bilayer tablet was carried out using USP dissolution apparatus type 1 (basked) at 50 rpm. The dissolution medium (900 ml) consists of 0.1 N HCL (pH 1.2) was used for the first hrs. and then replaced with phosphate buffer (pH 6.8) for the next 10 hrs., maintained at 37 ˚C, sink condition was maintained for the whole experiment. Samples (5 ml) were withdrawn at different time intervals, filtered and the drugs content in each sample was analyzed after suitable dilution using UV Spectrophotometer at λ_{max} for each drug respectively [18].

RESULTS AND DISCUSSION

Variables affecting the formulation of esomeprazole multi-particulate matrix tablets

All tablets contain 65% coated pellets, so 35% of excipient is needed to fill the void space between densely packed pellets in tablet formulation, although several researchers have used different percent of pellets (ranging from 10% to 90%) in preparation of tablets. The percent of pellets below 65% showed acceptable results [19]. Therefore in this study 65% of pellets were utilized in dosage form to ensure maximum protection of pellets by excipient/polymers.

1) Polymer Type

The pellets are typically coated with cellulosic/acrylic polymers. In the study, water insoluble, swellable, pH-independent directly compressible polymer; Eudragit RL and RS were used as a matrix for pellets and showed both acceptable mechanical properties and resistance to compaction with maintaining the integrity of pellets during compression into tablets [20]. Incorporation of ethyl cellulose to Eudragit polymer result in improve of mechanical strength and provide more flexibility in the compaction of pellets, this may be due to EC have good binding activity and plasticity, which undergo extensive plastic deformation even at low compression pressure [21].

2) Influence of Excipients

Tablets containing 65% pellets and 35% excipient blend in form of powder were prepared by direct compression process. MCC is mostly used excipient for direct compression technique, because MCC has good compaction and consolidated by plastic deformation, it will protect the coated particles better than other diluent [22]. Although using MMC PH 102 causes pellet segregation due to their large size difference, while using MCC PH 101 leads to chipping and friable tablet. So, combination of MCC PH 102 and PH 101 at a ratio 2:1 granulated by wet granulation optimizes the excipient blend and leads to successful compression of coated pellets. It was also observed that at least 35% of excipient should be compressed with the pellets, that proportion allowed the coated particles to embed freely into the matrix without segregation and to form into tablets, the same results were reported by Sateesh Sathigari and Yogesh C. Patheon during producing tablets of coated multi-particulates [23].

Evaluation of compressed amoxicillin and esomeprazole modified release layers:

The hardness of prepared matrix tablets that is shown in table (3) revealed variation which may be attributed to the difference in type and amount of retarding polymers in addition to other excipient added. The hardness increase as the amount of retarding polymer increase, this result may be attributed to the increase in compressibility of the matrix resulting from the higher polymer proportion [24]. Also the hardness increase when combination of two matrix forming polymers were used like HPMC with Xg and E-RS with EC, that resulted from increase in binding activity and interactions between particles (cohesion and

adhesion) due to increase in contact area bonding which improve compressibility of the matrix [25].

Friability is another measured of tablet's strength. All formulas have lost not more than 1% of their weight (except for S.CMC, which may be related to the smooth texture and hygroscopicity of S.CMC. [26]. On the other hands, all prepared formulas subjected to the drug content test complied with USP specification which is 90-110% of amoxicillin content in each individual tablet.

Table 3: Evaluation of post-compression parameters for amoxicillin and esomeprazole matrix tablets

Formula no.	**AM-1**	**AM-2**	**AM-3**	**AM-4**	**AM-5**	**AM-6**	**AM-7**	**AM-8**	**AM-9**	**AM-10**	**AM-11**	**AM -12**	**AM-13**
Hardness	4.6	4.9	5.4	5.8	6.7	6.9	7.4	7.6	9.3	9.7	9.9	10.2	7.3
Friability	1.3	1.1	0.95	0.8	0.82	0.76	0.6	0.61	0.47	0.46	0.44	0.39	0.76
Drug content	94.5	92.8	96.2	96.3	95.8	98.2	91.9	96.4	95.8	97.7	94.2	98.4	98.1
Formula no.	**ES-1**	**ES-2**	**ES-3**	**ES-4**	**ES-5**								
Hardness	4.5	4.4	4.1	5.2	5.5								
Friability	0.48	0.54	0.69	0.43	0.39								
Drug content	96.5	99.3	97.7	**101.5**	98.1								

Variables affecting the release profile from amoxicillin tablets

1) Effect of polymer type

Formula AM-3 was fabricated using S.CMC as retardant polymer, S.CMC-based matrix exhibited lower drug release retarding efficiency than other polymer, where faster dissolution and complete drug release has occurred at 3 hrs. these results might be attributed to the relatively lower viscosity of S.CMC which leads to low swellability and rapid dissolution and erosion of the diffusion gel layer. Furthermore, the disintegration properties of S.CMC might contribute to that effect [27]. While Drug release from formula AM-6 which contain HPMC K100M was slowest than other formulas, owing to its higher viscosity which can strengthen the gel layer around the tablet and retard the penetration of water into the drug matrix core, results in decrease in the release rate due to decrease in the total porosity within the matrix. Additionally HPMC have higher hydration and larger degree of swelling compared to other cellulose polymers [28]. Figure (1) exhibits the effect of polymer type.

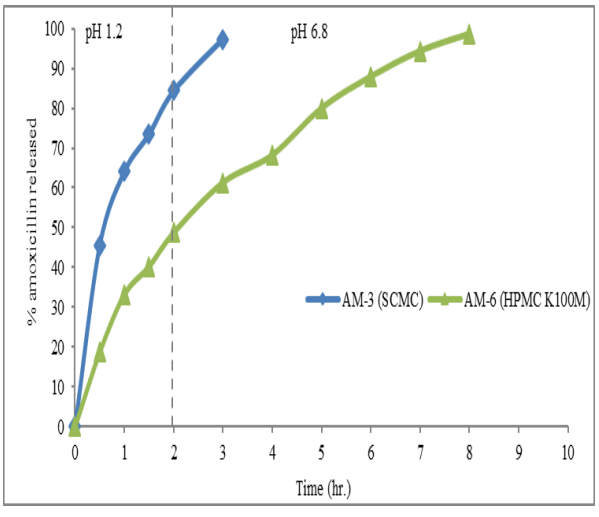

Fig. 1: The effect of polymer type on the cumulative release of AMT at 37°C

2) Effect of polymer concentration

Figure (2) show the release profiles of Formulations containing S.CMC; (AM-1,AM-2 and AM-3) by increasing the amount of polymer used (from 15% to 20% then 25% w/w) produces non-significant decrease ($p>0.05$) in the amount of drug released, as these formulations released their entire content completely in the first 1-3 hrs. This fast release profile is because of the presence of ionized carboxylic acid groups in S.CMC, which causes rapid dissolution and disintegration [29]. On the other hand, this effect could be attributed to the fact that CMC did not fully hydrate to form a gel when placed in a media with low pH (e.g. pH 1.2) [30].

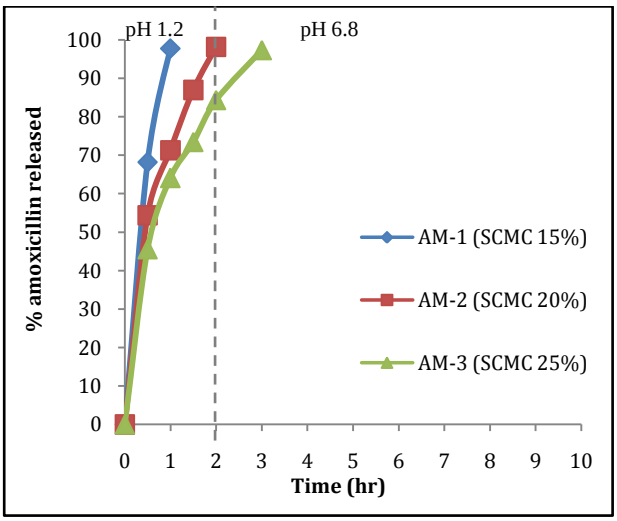

Fig. 2: The effect of S.CMC concentration on the cumulative release of AMT at 37°C

Formulas AM- 4, 5 and 6 were prepared to show the effect of different amount of HPMC used on the release profile; formula AM-4 where prepared employing 15% w/w of HPMC, about 80% of the drug released in the first 3 hrs. and sustained release profile was not observed. Faster release of drug may be due to the faster dissolution of the drug through the less viscose gel barrier due to low concentration and it's diffusion out of the matrix forming pores for the entry of the solvent molecules [31]. By increasing the HPMC percentage as in formulas AM-5 and 6, a viscose gel layer is formed, resisting to erosion and the diffusion of the drug is controlled primarily by the gel viscosity, therefore gel barrier and longer diffusional path may lead to decrease in the diffusion and then drug release from polymer [32].

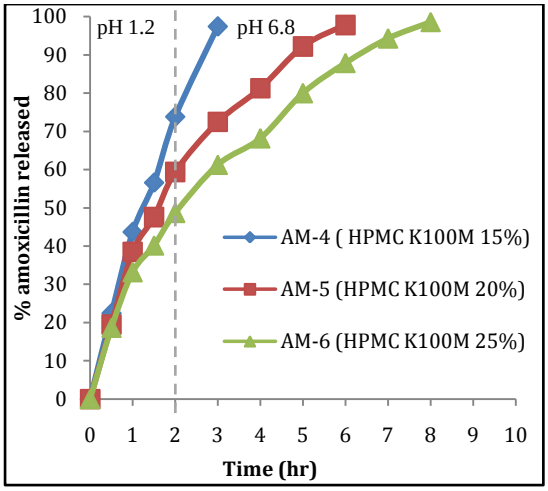

Fig. 3: The effect of HPMC K100M concentration on the cumulative release of AMT at 37 ˚C

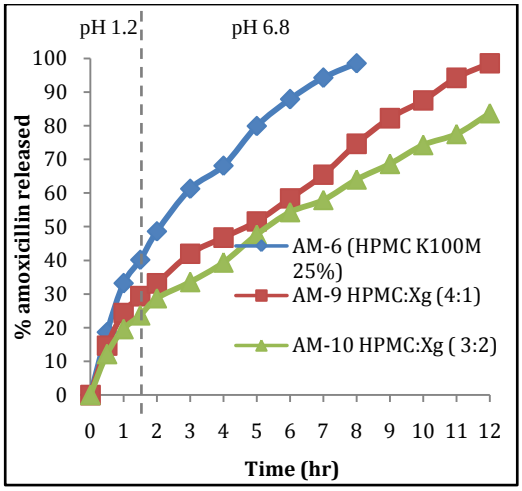

Fig. 5: The effect of different ratio of HPMC:Xg combination on the cumulative release of AMT at 37˚C

3) **Effect of polymer combination and ratio**

Formulas (7, 8) and (9, 10) were designed to study the effect of incorporation of carbapol (Cp.) and xanthan gum (Xg) respectively on the release profile of amoxicillin. Addition of Cp. to HPMC leads to reduction in the amount of amoxicillin released from the matrix tablets, in comparison with formula AM-6 which contain no Cp. This is probably resulted from combination of anionic polymer (Cp.) with nonionic polymer (HPMC) produces a synergistic increase in viscosity, and therefore gel strength of the matrix, through stronger hydrogen bonding between the carboxyl groups of Cp. and hydroxyl groups of HPMC, leading to stronger cross-linking between the two polymers and slow drug diffusion can occurs [33], the results are shown in figure (4).

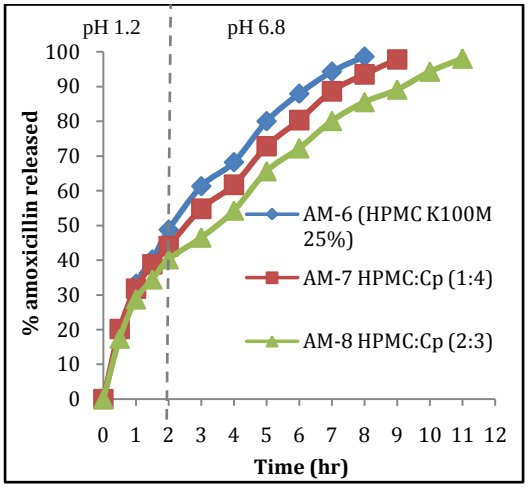

Fig. 4: The effect of different ratio of HPMC: Cp. combination on the cumulative release of AMT at 37˚C

At the same time, addition of Xg to HPMC in formula AM-9 and AM-10 produce significant decrease on the release of amoxicillin from the matrix as shown in figure (5). It has been reported that incorporation of Xg. in HPMC matrix system can form very thick gel which could maintain constant drug release for a considerable period of time and preserve physical integrity of the tablet in the release-medium to achieve a desirable prolonged release pharmacokinetic profile, therefore formula containing Xg. (quick gelling tendency) in combination with HPMC (high gelling ability) show strong retardation than formulas containing HPMC alone [34].

4) Effect of diluent type

Replacement of lactose with DCP leads to reduction of drug release from compressed matrix but in a non-significant manner ($p>0.05$). This change in drug release could be interpreted by as lactose is water soluble filler; it increases the hydration rate and relaxation of the polymer chains resulting in more dissolved drug diffusing out from the matrix. Moreover, this soluble substances act as channeling agent by rapidly dissolving and easily diffusing outward, therefore decreasing tortuosity and/or increasing the matrix porosity. On the other hand, dicalcium phosphate is water insoluble and non swellable filler; hydrophobic in nature, has no effect on swelling, erosion and hydration of HPMC. Therefore the slower release rate of amoxicillin is the direct result for the presence of an insoluble additive in the matrix [35]. The release profiles are shown in figure (6).

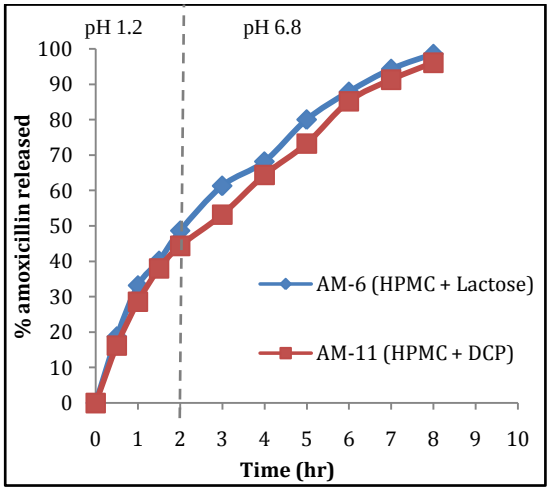

Fig. 6: The effect of diluent type on the cumulative release of AMT at 37˚C

5) **Effect of binder type**

Replacement of acacia as binder in formula AM-9 by PVP in formula AM-12 produce comparative results in the rate and extend of drug release from matrix tablets, as both formulations showed complete drug release at the end of 12hrs. as shown in figure (7). However tablets prepared using PVP K30 in isopropyl alcohol as granulating solution showed fast release in initial phase and slight reduction of drug release in last phase of dissolution time compared to formula

prepared using acacia as granulating agent. This effect may be referred the higher solubility of PVP in media with different pH, allowed penetration of the medium into the matrix and more rapid release of amoxicillin [36], also could be attributed to disintegrating property of acacia gum [37].

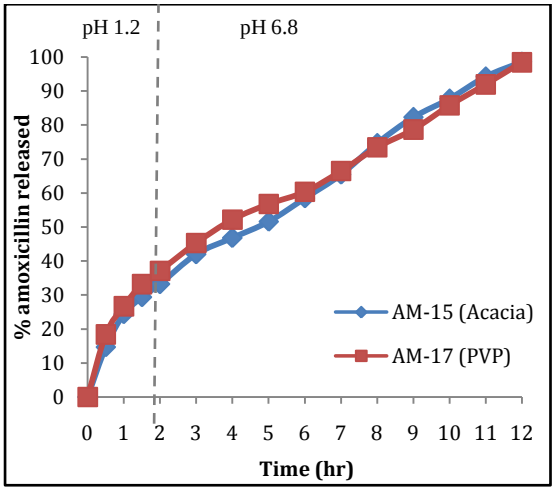

Fig. 7: The effect of binder type on the cumulative release of AMT at 37 ˚C

6) Effect of method of preparation

To examine the influence of method of preparation on the release profile, formula AM-12 which prepared by wet granulation technique was compared with formula AM-13 that prepared by direct compression and the results represented in figure (8). The release profile of the drug was slower in case of wet granulation; this could be due to improved distribution of the polymers around drug particles, which in turn slows down penetration of water into the granules and/or reduces the direct contact of the drug with the dissolution medium, while the direct compression process will provide matrix with a higher porosity and thus faster drug release than the granules obtained via a wet granulation process [38]. Similar results were obtained on diclofenac sodium release (Savas *et. al.*) [39], from tablets matrices where wet granulation technique was compared to direct compression technique.

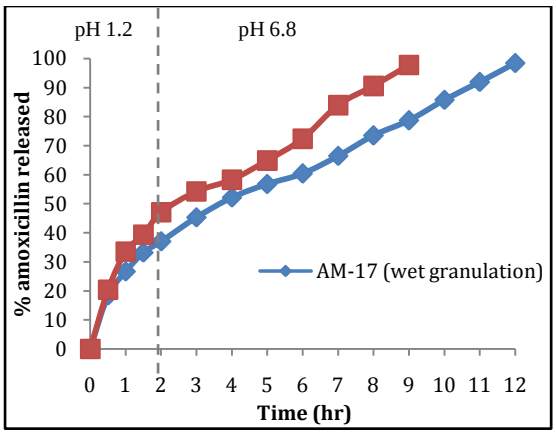

Fig. 8: The effect of method of preparation on the cumulative release of AMT at 37˚C

Selection of the best formula of amoxicillin matrix tablet

Formula AM-12 (which contain HPMC:Xg. in ratio of 4:1 and PVP as a binder) showed the most suitable sustained release period for 12 hrs., thus can be given twice daily, that controls the drug release in the initial hours beside making the formulation release a high cumulative amount of drug at the end of 24 hrs., maintaining effective concentration for longer time of a day and preventing drug free interval between doses. This can be useful to achieve the therapeutic benefits at low doses of the API thus can help in improving the treatment of ulcer and enhancing patient compliance [40]. So, it will select for preparation of bilayer tablet.

Variables affecting release profile from esomeprazole multi-particulate matrix tablets

1) **Tableting of enteric coated pellets (peltab)®**

The release profile of multi-particulate tablets comprised of enteric coated esomeprazole-pellets is shown in figure (9). It was seen that acceptable delayed dissolution data was achieved with a maximum of approximately 5% drug being lost in 0.1 N HCL solution after 2 hrs., and 90% of drug being released within 50 min after exposure to basic medium.. The results of dissolution study meet the USP specification for delayed release (enteric coated) dosage forms, which state that; no individual value should exceed 10% when dissolved in the acidic phase after 2 hrs. of operation and not less than 75% should be released in basic buffer solution after continuous operation on the apparatus for 45 min [41].

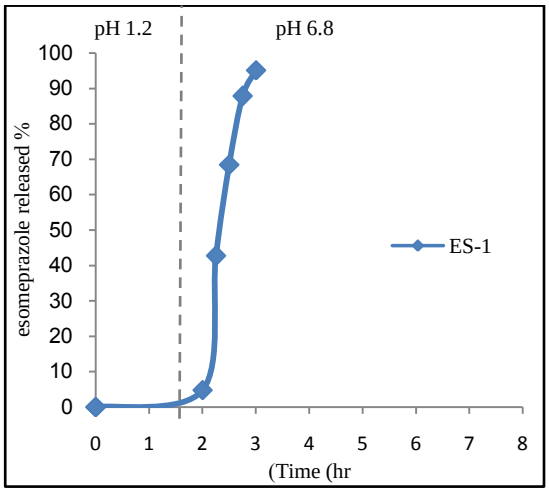

Fig. 9: the release profile of ES from compressed multi-particulate tablets at 37 ˚C

2) **The effect of polymer type**

Figure (10) shows the release profile of formulas ES-2 and ES-3 which contain 20% w/w of tablet weight of E-RL and E-RS respectively, it appears that E-RS possess a better retardation rate than E-RL. This variation related to the higher permeability of E-RL than that of E-RS polymer type, this effect could be explained by considering the chemical structure of Eudragit polymers. The Eudragit RL and RS are synthesized from acrylic and meth acrylic acid esters with high and low content of quaternary ammonium groups (0.2 and 0.1) respectively, the ammonium groups are present as salts and are responsible for the permeability of the polymer [42]. These results were in consistent with those obtained by Sahib *et. al* [43] who found that both types of Eudragit exhibit significant release retardation but E-RS is more suitable than E-RL in decreasing drug release.

3) **The Effect of Addition Ethyl cellulose**

The addition of 5% w/w (formula ES-4) and 7.5% w/w (formula ES-5) of EC produce significant decrease in drug release rate and showed the desired release profile over extended period compared with the formula free of EC (formula ES-3) These results are in agreement with Tabandeh *et. al* [21]. This effect could be attributed to several effects; EC have tendency to mask the quaternary

ammonium groups present in E-RS to some extent, also water repelling property of EC, beside more rigid complex formed by Eudragit in presence of EC, and the pore network in hydrophobic polymer become more tortuous resulting in slower penetration of dissolution medium and/or slower release of dissolved drug.

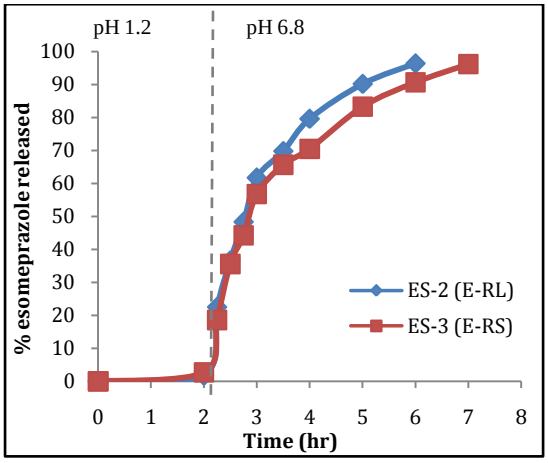

Fig. 10: The effect of polymer type on the release profile of ES at 37 ˚C

At the same time partial replacement of MCC possess disintegrating property with EC have tablet binding activity result in keeping the matrix integrity for longer time, and providing more controlled and extended release rate of esomeprazole from multi-particulate tablet [44].

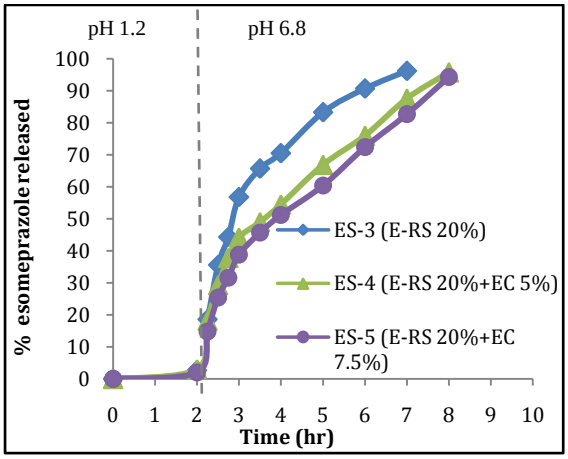

Fig. 11: The effect of addition EC at different ratio into 20% Eudragit-RS concentration on the release profile of ES at 37˚C

Selection of the best formula of esomeprazole multi-particulate tablets

According to similarity factor (f_2), formula ES-5 (which contain 20% w/w E-RS and 7.5% w/w EC) was the best formula as shows the higher similarity (71.45) comparing to the reference release of enteric coated tablets of esomeprazole, the release profiles of the suggested formula and the reference standard is shown in figure (12). Thus formula ES-5 was selected for the further bilayer tablet formulation with optimized formula of amoxicillin layer.

Determination of the Release Kinetics

The release of amoxicillin and esomeprazole from the optimized formulas (AM-12 and ES-5 respectively) was determined by finding the best fitting of the dissolution data to the mathematical models like zero order, first order, Higuchi's model, and the results are shown in table (4). It has been observed that both layers showed a good fitting to Higuchi model of drug release. However, to confirm the exact mechanism of drug release the dissolution data was fitted to Koresmeyer empirical equation and the release exponent ***n*** show far different values between the two layers (0.517 for amoxicillin and 1.5 for esomeprazole), this result can be explained according to the nature of matrix former used in each layer. The value of ***n*** for amoxicillin layer is between 0.45-0.89 which suggesting anomalous transport where two or more phenomenon are involved in drug transport, for esomeprazole layer the ***n*** value is more than 0.89 suggesting super case II transport (two or more mechanisms were involved including diffusion.

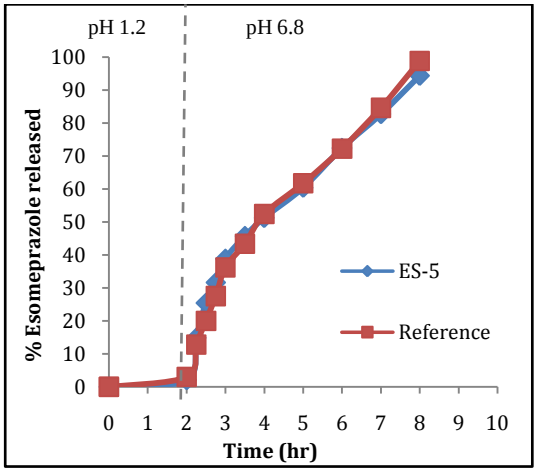

Fig. 12: The release profile of ES of selected formula (ES-10) versus reference release of enteric coated core tablet at 37˚C

Bilayer tablets preparation

Formula AM-12 was chosen as optimized formula for amoxicillin sustained release layer while formula ES-5 was chosen as optimized formula for esomeprazole controlled release layer, 900 mg granules of amoxicillin layer were manually poured into 12 mm die and mild compressed (compression force 4 tones), over this compressed layer, 400 mg physical blend of esomeprazole layer were poured into the die above the amoxicillin layer and subjected to final compression (compression force 4 tones) with dwell time of 15 second to get bilayer tablets.

Evaluation of bilayer tablet

The hardness value was found to be 10.6 kg/cm^2 for amoxicillin layer which was more as compared to individual layer because of it subjected to double compression. While for esomeprazole layer the hardness was 5.4 kg/cm^2. The friability was 0.73% for bilayer tablet which was increased as compared to individual layers because of increase in amount of excipients included in tablet formulation. Lisinopril and Gliglazide exhibit the same results when formulated as bilayer tablet [45]. Also Assay of amoxicillin and esomeprazole in the bilayer tablet was found that amoxicillin content was about 98.3% and esomeprazole amount was 97.8% which complies with the USP limits (90-110%).

Bilayer Tablet's Dissolution Study

Dissolution study was performed for prepared bilayer tablets and the results are shown in figure (13) and (14) for amoxicillin and esomeprazole respectively. There is no significant difference in the release profiles of amoxicillin and esomeprazole from bilayer tablet in comparison with amoxicillin sustained release layer and with esomeprazole extended release enteric multi-particulate matrix alone. Although the polymers used in fabrication of bilayer matrix tablet are pH-independed hydrophilic polymer. They differ in hydration rate, swelling capacity and molecular weight thus

viscosity of the formed gel layer, This phenomenon result in rapid and complete layers separation upon contact with dissolution medium, so the surface area subjected to dissolution media was not largely changed and the release behavior for both drugs from bilayer tablet was not significantly different from separated layer release profile.

Table 4: drug release kinetic parameters for amoxicillin and esomeprazole from selected formulas

Selected	Zero order		First order		Higuchi		Korsmeyer-peppas		
Formula	K0	R2	K1	R2	KH	R2	Kkp	R2	n
AM-17	6.398	0.987	-0.248	0.791	27.54	**0.989**	26.48	0.997	0.517
ES-10	12.55	0.969	-0.395	0.922	54.53	**0.984**	5.62	0.855	1.5

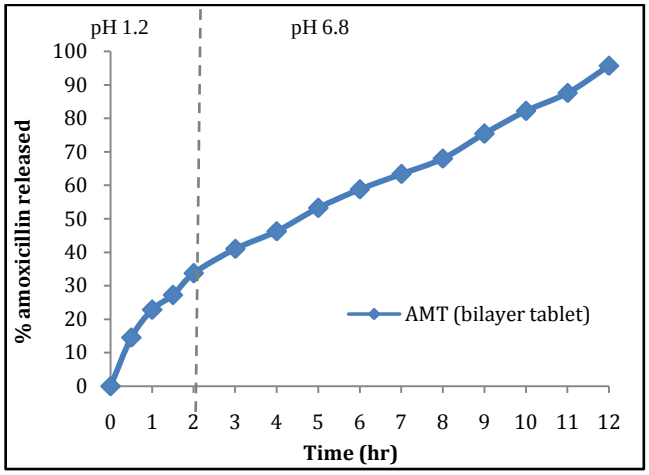

Fig. 13: The dissolution profile of AMT from bilayer tablet at 37˚C

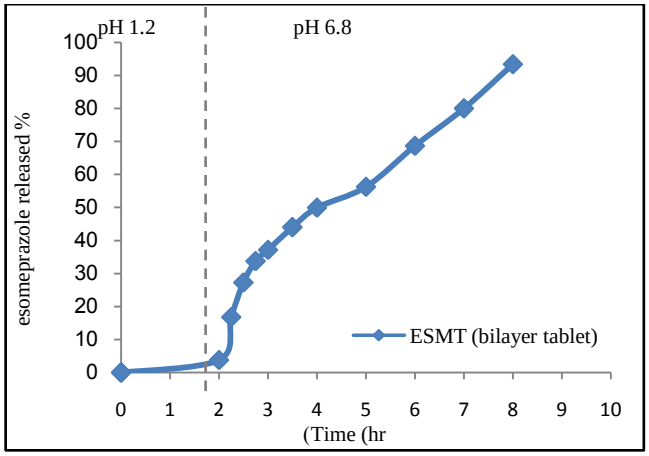

Fig. 14: The dissolution profile of ES from bilayer tablet at 37˚C

REFERENCE

1. Pinto J.F., Site-specific drug delivery systems within the gastro-intestinal tract: From the mouth to the colon. International Journal of Pharmaceutics 2010; 395:44-52.
2. Rasheed S., Arief M., Vani P.S., Gajavalli S.R., Venkateswarlu G., vineela P., Anjanejulu N., Kishore R.N., Formulation and evaluation of sustained release tablets of bupropion hydrochloride. Research Journal of Pharmaceutical, Biological and Chemical Sciences 2010; Vol1 (4): Page No. 1018.
3. Ansel H., Allen L., Popovich N. Modified Release Dosage Form and Drug Delivery Systems.8th ed. Lippincot, Williams, and Wilkins. 2005; p.227-260.
4. Rohan D. Deshpande, D. V. Gowda. Bi-Layer Tablets- an Emerging Trend: A Review. International Journal of Pharmaceutical sciences and Research 2011; vol2 (10):2534-2544.
5. V.N. Shrikhande, Pankaj P. Ostwal. Formulation and Evaluation of Bi-layer tablet. Authorstream Sep. 2011.
6. Putta R. K., Hiremath D., S. Rajendra Reddy. Design and Evaluation Studies on Floating Tablets for Peptic Ulcer Treatment. Journal of Advanced Pharmacy Education & Research.
7. M. S. Lakshmi, P. Ram kumar, M. Mohen, Formulation and evaluation of gasroretentive mucoadhesive granules of Amoxicillin Trihydrate against H. Pylori. Journal of Pharmacy Research: 2012; 5(6): 3692-3705.
8. Marulla R. K., K.G. Parthiban, Nelluri R., Nagapuri S.D., Perumulla A. Formulation and evaluation of floating drug delivery system of amoxicillin trihydrate. International Research Journal of Pharmacy. 2012; 3(8).
9. Abbaspour, F. Sadeghi, H. Afrasiabi Garekani. Design and study of Ibuprofen disintegrating sustained-release tablets comprising coated pellets. European Journal of Pharmaceutics and Biopharmaceutics. 68(2008): 747-759.
10. 10.V.S.N. Murthery Dwibhashyma, J. Vijaya Ratna. Key formulation variables in tableting of coated pellets. Indian J. Pharm. Sci. 2008; 70(5): 555-564.
11. 11.Sailesh, Teg Kmurthy, Pavan Kumar Sam. Compression of coated multiparticulates. Pharmaceutical Information. Pharmainfo.net. 2010.
12. Torrado JJ., Augsburger LL. Effect of different excipient on the tableting of coated particales. Int. J. Pharm. 1994; 106: P. 149-155.
13. 13.Costa P., Sousa J. Modeling and comparison of dissolution profiles. European Journal of Pharmaceutical Sciences 13 (2001): 123-133
14. M.L. Vueba, L.A.E. Batista de Carvalho, F.Veiga, J.J. Sousa. Influence of cellulose ether polymer on Ketoprofen release from hydrophilic matrix tablets. Eur. J. Pharma. Sci. 58 (2004): 51-59.
15. Shiyani B., Gattani S. Formulation and Evaluation of Bi-layer Tablet of Metoclopramid Hydrochloride and Ibuprofen. AAPS PharmSciTech 2008; Vol. 9, No. 3.
16. Vogesh P. A., Surya P. G., Ajay V., Mona Y. A., Arun K. Gupta. Simultaneous estimation of Esomeprazole and Levosulpiride in solid dosage form. Pelagia Research Library. 2012; 3(3): P. 337-342.
17. Yuvraj Singh D., Murari Lal S., Kamta Prasad N. A UV Spectrophotometric method developed for the simultaneous estimation of Amoxicillin trihydrate and Ranitidine bismuth citrate for Helicobacter Pylori infections Pelagia Reseasrch Library Der Pharmacia Sinica, 2010; 1 (3): 11-16.
18. Abbaraju Prasanna L., Ajay Kumar B., Arun Kumar G. Formulation and Evaluation of Levofloxacin hemihydrate and Ambroxol HCL Bilayer Tablets. Asian Journal of Pharmaceutical and Clinical Research. 2012:Vol. 5, Supple 4, 273-277.
19. Debunne, C. Vervact, D. Mangetings, J. P. Remon. Compaction of enteric-coated pellets: influence of formulation and process parameters on tablet properties and in vivo evaluation. European Journal of Pharmaceutical Science. 22(2004): 305-314.
20. M.R. Abbaspour, F. Sadeghi, H. Afrasiabi Gorekani. Thermal treating as a tool to produce plastic pellets based on Eudragit RS PO and RL PO aimed for tableting. Eur. J. Pharma. Biopharma. 67 (2007): 260-267.
21. Hosseinali Tabandeh, Seyed Alireza M, Tina B. G. Preparation of sustained-release matrix tablets of aspirin with ethyl cellulose, eudragit RS100 and eudragit S100 and studying the release profiles and their sensitivity to tablet hardness. Iranian Journal of Pharmaceutical Research (2003): 201-206.

22. Hiren P. Patel, J. K. Patel, Ravi R. Patel, Manish P. Patel, PELLETS: A GNERAL OVERVIEW. International Journal of Pharma World Research, 2010.Vol. 1, Issue 2.
23. Sateesh Sathigari, Yogesh Chachare Patheon. Formulating and Producing Tablets Containing Large Coated Multiparticulates. CSC, Tablets & capsules, March 2013.
24. Samer H. Aziz, Alaa A. Abdulrasool, Ahmed A. Hussein. Factors affecting the formulation of Carbamazepine extended release tablet. Iraqi Journal of Pharm. Sci. 2008; vol. 17(1).
25. Kerly F. M., Jose Aparicio B. F., Fabiana E. B., Cristiane de D. Kratz. Development and Evaluation of Amoxicillin Formulation by Direct Compression: Influence of the Adjuvants on Physicomechanical and Biopharmaceutical Properties of the Tablets. Acta farm. Bonaerense, 2005; 24(1): p. 39-47.
26. K. Ragharam Reddy, Srinivas Mutalik, Srinivas Reddy. Once-daily sustained release matrix tablets of Nicorandil: formulation and in vitro evaluation. AAPS PharmSciTech. 2003; 4(4),Article 61.
27. Hamdy abdelkader, Ossama Youssef Abdalla, Hesham Salem. Formulation of Controlled-Release Baclofen Matrix Tablets: Influence of some Hydrophilic Polymers on the Release Rate and in vitro Evaluation. AASP Pharm.Sci.Tech. 2007; 8(4): article 100.
28. Rahman M., Roy S. Evaluation of Various Grade of Hydroxypropyl Methylcellulose Matrix System as Oral Sustained Release Drug Delivery System. Journal of Pharmaceutical Science and Research 2011; Vol.3 (1).
29. Jaber Emami, Mona Tajeddin, Fatemeh Ahmadi. Preparation and In Vitro Evaluation of Sustained-Release Matrix Tablets of Flutamide Using Synthetic and Naturally Occuring Polymers. Iranian Journal of Pharmaceutical Research 2008; 7 (4): 247-257.
30. Shady M., Maha M. Amin, Omaima N., Nabaweya A. Abd el gawad. Salbutamol Sulphate Controlled Release Hydrophilic Matrix Tablets. RGUHS J. of Pharma. Science 2011; Vol. 1, Issue 3.
31. D. B. Raju, S. M. M. Kiran Babu, M. M. Varma. Design Development and Evaluation of Extended Release Tablets of Alfuzosin Hydrochloride. Journal of Chemical and Pharmaceutical Research. 2010; 2(2): 90-96.
32. Victoria M., James L., Philip R. Influence of drug: hydroxypropyl methylcellulose ratio, drug and polymer particle size and compression force on the release of Diclofenac sodium from HPMC tablets. Journal of Controlled Release 1999; 57: 75-85.
33. Mehrgan H., Mortazavi S. The Release Behavior and Kinetic Evaluation of Diltiazime HCL from Various Hydrophilic and Plastic Based Matrices. Iranian Journal of Pharmaceutical Research. 2005; 3: 137-146.
34. Mukesh C. Gohel, Rajesh K. Parilkh, Stavan A. Nagori, Dillip G. Jena. Fabrication of Modified Release Tablet Formulation of Metoprolol Succinate using Hydroxypropyl Methylcellulose and Xanthan Gum. AASP PharmaSciTech. 2009. Vol.10, No.1, march.
35. Bendgaude Namdeo T., Iyer Vidaya R., Poddar Sushi I. S. The Effects of Lactose, Microcrystalline Cellulose and Dicalcium Phosphate on Swelling and Erosion of Compressed HPMC Matrix Tablet: Texture Analyzer.Iranian Journal of Pharmaceutical Research 2010; 9(4): 349-358.
36. Hubertus Folttmann, Ansiul Quadir. Polyvinylpyrrolidone (PVP)-One of the most widely used excipients in pharmaceuticals: an overview. Drug Delivery Technology, June 2008; Vol. 8, No. 6.
37. Anoop K. S., Vipul K. S., R. Panner Selvam, T. Sivakumar. Evaluation of mangifera indica gum as tablet binder. International Journal of PharmTech Research 2010; vol. 2, no. 3: p. 2098-2100.
38. Diego Gallardo, Brigitte Skalsky. Controlled Release Solid Dosage Forms Using Combinations of (meth)acrylate Copolymers. Pharmaceutical Development and Technology 2008; 13: 413-423.
39. Tanbir A., Moynul H., Saiful I., Muhammad R., Habibur R., Effect of Granulation Technique and Drug-Polymer Ratio on Release Kinetics of Gliclazide from Methocel K4M Matrix Tablet. Bangladesh Pharmaceutical Journal 2010. Vol. 13, No. 2.
40. Jayvadan K. Patel, Madhabhai M. Patel. Stomach Specific Anti-Helicobacter Pylori Therapy: Preparation and Evaluation of Amoxicillin-Loaded Chitosan Mucoadhesive Microspheres. Current Drug Delivery, 2007, Vol. 4, No. 1: 41-50.
41. Jerome A. Chris J.J., Karsten S., Omeprazole MUPS® An Advanced Formulation Offering Flexibility and Predictability for Self-Medication. SelfCare, the Journal of consumerted health. 2011; 2(S1): 1- 14.
42. Pao-Chu Wu, Yaw-Bin Huang, Chia-Hung Sung, Ren-Jiunn W., The Effect of Eudragit and Enteric Polymer Composition on the Release of Nicardipine. Journal of Food and Drug Analysis. 2006: vol. 14, no. 4, p. 334-339.
43. Mohanad N. Sahib, Shaymaa A. abdul Ameer, Alaa A. Abdul Rasool. Design and in vitro evaluation of Prednisolone tablets as a potential colon delivery system. Asian Journal of Pharmaceutical and Clinical Research. 2009; vol. 2, issue 4.
44. Kambham Venkateswarlu, A. Shanthi. Formulation and Evaluation of Sustained Release Glipizide Matrix. IOSR Journal of Pharmacy and Biological Science 2012; Vol. 2, Issue 5: pp. 17-23.
45. Izhar Kasid, M. A. Saleem, Rozeen Parveen, Nikhat Parveen, Development of bilayer tablets of Lisinopril and Gliclazide: in vitro and in vivo evaluation. Scholars Research Library. Der Pharmacia Lettre, 2013; 5(2).