doi.org/10.36721/PJPS.2020.33.1.REG.071-077.1

Blend of guar gum and Eudragit shows excellent drug release retarding behavior in sustained release tablets

Sarah Ahmad[1], Muhammad Jamshaid[1], Rizwan Mehmood[2], Irfan Bashir[1], Rabia Ali[1] and Sana Jameel[1]

[1]Faculty of Pharmacy, University of Central Punjab, Lahore, Pakistan
[2]CCL Pharmaceuticals, Lahore, Pakistan

Abstract: The objective of the current study was to compare sustained release behavior of natural and synthetic polymers in matrix tablets of lisinopril and hydrochlorothiazide combination. Guar gum was used as a hydrophilic natural polymer while Eudragit L 100-55 was used as synthetic polymer. Tablets were formulated by direct compression method using different ratios and combinations of both polymers. Various physical tests were performed. After that, *in vitro* drug release patterns were investigated by performing dissolution in pH 6.8 phosphate buffer. Results indicated that tablets with combination of both guar gum and Eudragit L 100-55 (formulation F10) were having the best drug release retarding behavior. All formulations followed zero order kinetics indicating the drug release was independent of the concentration. Higuchi model revealed drug release by diffusion mechanism while Korsmeyer Peppas model suggested that formulations followed the non-fickian release behavior.

Keywords: Hypertension, modified release, Eudragit L 100-55, natural polymer, higuchi model, drug release.

INTRODUCTION

Lisinopril, known as *(2S)-1-[(2S)-6-Amino-2-[[(1S)-1-carboxy-3 phenylpropyl] amino] hexanoyl] pyrrolidine-2-carboxylic acid dehydrate* (B.P, 2013),(fig. 1) is an oral long acting angiotensin converting enzyme (ACE) inhibitor which is primarily used for the treatment of hypertension, congestive heart failure, and heart attacks (Patil *et al*., 2012, Nagendrakumar *et al*., 2013, Derayea *et al*., 2017, Şenkardeş *et al*., 2017) especially in diabetic patients and also plays a vital role in the management and prevention of diabetes complications such as diabetic nephropathy and retinal complications of diabetes (Kasid *et al*., 2013, Jagdale *et al*., 2014, Şenkardeş *et al*., 2017). The dose of the lisinopril is 2.5 to 20 mg (Viswanadhan *et al*., 2012).

Hydrochlorothiazide (HCT) is a thiazide diuretic. Chemically, it is *6-Chloro-3,4 -dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide* (B.P, 2013) (fig. 2). HCT is useful for treating mild to moderate essential hypertension as well as enhancing the antihypertensive efficacy of multidrug regimens. It is used to treat edema associated with heart, liver and renal diseases (Brunton *et al*., 2011). According to a study, starting doses of HCT should be 12.5 mg in the elderly and 25 mg in younger patients, with a maximum dose of 50 mg/day (Brunton *et al*., 2011, Ratilal *et al*., 2011). Combination therapy has now become a standard line of treatment for hypertension to reduce the burden of cardiovascular morbidity and mortality. Sustained release tablets with a safer and most widely used combination of an ACE inhibitor (Lisinopril) along with a Thiazide diuretic (Hydrochlorothiazide) are considered to be drug of choice for controlling blood pressure effectively than using drugs individually (Shah *et al*., 2017). This combination offers low dose regimen by using multiple drugs rather than a high dose regimen with a single drug, thus, reducing dose related side effects and controlling blood pressure effectively (Brunton *et al*., 2011).

Sustained release matrix tablets were formulated using direct compression method. It is the latest technique which involves only blending and compression (fig. 3). Two types of polymers were used in the study i.e., natural hydrophilic polymer (guar gum) and synthetic polymer (Eudragit L 100-55).

Swellable hydrophilic matrix systems may be natural gums (tragacanth, guar gum), semisynthetic (HPMC, CMC) or synthetic polyacrylamides. Drug release from such hydrogels involves hydration of matrix, gel formation, gum swelling and drug release by swelling monitored diffusion process (Dinda, 2011). Out of these, natural polymers are abundantly used for sustained release preparations as they are non-toxic, cheap and bio-compatible. Guar gum (GG) is used in SR matrix tablets replacing cellulose derivatives like methyl cellulose. Also, it is used as disintegrant, binder or as controlled release polymer in tablets. Where natural polymers are used for sustained release effects, some synthetic polymers e.g., poly methacrylates are also used in matrix systems. Hydrophilic synthetic polymers release the drug through the process of diffusion. They can be water soluble synthetic polymers, Synthetic biodegradable polymers or Synthetic non-biodegradable polymers (Dinda, 2011).

*Corresponding author: e-mail: sara.ahmad@ucp.edu.pk

Eudragit L 100-55 is a copolymer of methacrylic acid and ethyl acrylate. Large quantities (usually 5% to 20%) of dried polymer are added for controlling drug release from matrix tablets. The objective of this study was to develop sustained release matrix tablets of lisinopril and hydrochlorothiazide combination and compare sustained release behavior of natural polymer (guar gum) with synthetic polymer (Eudragit L 100-55).

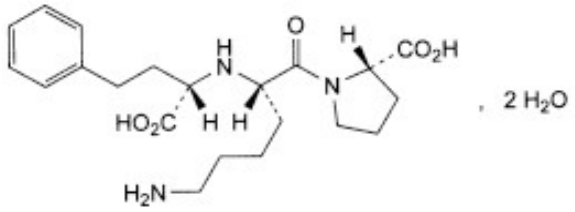

Fig. **1**: Structure of Lisinopril dihydrate adapted from (B.P, 2013)

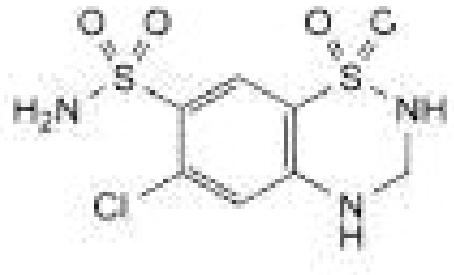

Fig. **2**: Structure of Hydrochlorothiazide HCl adapted from (B.P, 2013)

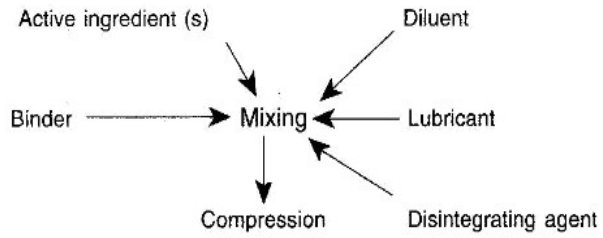

Fig. **3**: Direct compression technique adapted from (Agarwal and Kaushik, 2012)

MATERIAL AND METHODS

Lisinopril dihydrate and Hydrochlorothiazide HCl were gifted from Highnoon Laboratories. Other ingredients like Guar gum, Eudragit L 100-55, magnesium stearate, aerosil and lactose were obtained from E Merck Germany. Other chemicals used in evaluation (HCl, Phosphate buffer tablets) were obtained from E Merck Germany. All chemicals were pure and were of analytical grade.

Direct compression technique was used to formulate sustained release matrix tablets. Lisinopril and hydrochlorothiazide were active ingredients comprising 16.25% of the formulation. Both the polymers were used in 8-32% concentration depending on the formulation type. Magnesium stearate was used as lubricant up to 0.25%. Aerosil was incorporated as tablet disintegrant and glidant in the ratio of 0.1%. Lactose was used as a diluent in concentrations of 50-75% in different formulations. Table 1 shows the composition of different formulations.

All ingredients were weighed separately on an electronic balance. Then, active ingredients and polymers were passed one by one through sieve no.60 to achieve uniformity of particle size. The polymers and active ingredients were added to a polythene bag and mixed for 15 minutes. Then added lactose and mixed for 5 minutes. Then, colloidal silicon dioxide/aerosil and magnesium stearate were added for lubrication and again mixed for 5 minutes. Finally, blend was filled into the hopper of a single punch compression machine (RUD Compression Machine). The weight of the tablets was adjusted to 200 mg and then powder was compressed into tablets. Throughout compression, tablets were tested physically for hardness, thickness, diameter, weight variation and friability.

Hardness test

Hardness is defined as "the force required for breaking the tablet". Ten tablets were taken randomly from each formulation and hardness was determined using digital hardness tester (Curio 2020) in kg/cm^2 (Ijaz *et al*., 2013, Kannan *et al*., 2012). Hardness for sustained release tablets should be within limits of (4-11 kg / cm^2).

Friability test

This test indicates "the capability of the tablet to hold up the mechanical shock while handling". Roche Friabilator (Galvano Scientific Friability tester Model FT-L) was used to evaluate the friability. 20 tablets were taken from each formulation. Percentage friability was calculated by using formula:

$$\% \text{ age friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

A maximum loss of mass (obtained from a single test or from the mean of 3 tests) not greater than 1.0 per cent is acceptable for most products (B.P, 2013).

Weight variation test

This test proposes the individual variation of weight in the tablets. Twenty tablets were randomly taken and individual weight was noted. The average weight was calculated. Individual tablet weight was compared with average weight. NMT 2 of the individual weights should deviate from the average weight by more than the % variation indicated in table in BP and none should deviate

by more than twice that % (Kannan *et al*., 2012). Weight variation was calculated by:

$$\% \text{ variation} = \frac{\text{Average weight} - \text{Individual weight}}{\text{Average weight}} \times 100$$

In-vitro drug release

The percentage release of lisinopril and hydrochlorothiazide from sustained release tablets was calculated using USP Dissolution Testing Apparatus II (Paddle method). 900ml of the dissolution medium (0.1 N HCl) maintained at 37±0.5°C was used. One tablet was placed in each of the six vessels and speed of paddles was adjusted at 50 rpm. 5ml sample was collected after 30 minutes, 60 minutes and 120 minutes. After that, 0.1 N HCl was replaced by freshly prepared pH 6.8 buffer maintained at 37±0.5°C. Samples were withdrawn after each hour up to 10 hours or until the tablets were completely dissolved. Absorbance of each sample was noted at the respective wavelengths of drugs (215 nm for lisinopril and 273nm for hydrochlorothiazide) and compared with the standard using UV double beam Spectrophotometer (Dynamica Halo DB-20 Series). The % release was determined by:

$$\% \text{ Drug release} = \frac{\text{Absorbance of the sample}}{\text{Absorbance of the standard}} \times 100$$

Drug release kinetics

In order to evaluate the release kinetics of drug, data obtained from *in vitro* dissolution at different time intervals were fitted in kinetic models like zero-order ($C = k°t$), first-order ($\text{Log } C = \text{Log } C° - k\ t / 2.303$), Higuchi model ($Qt = kH\ (t)\ 0.5$) and Korsmeyer Peppas model ($Mt / M^oC = Ktn$**)**. The n value was used to characterize different release mechanisms like n <or=0.45 indicates Case- I or Fickian Diffusion, 0.45<n< 0.89 indicates Anomalous (non-Fickian) diffusion, n=0.89 indicates Case-II transport (zero order release) and n>0.89 indicates Super case-II transport (Dash *et al*., 2010, Singhvi and Singh, 2011, Chime *et al*., 2013). Then values of correlation coefficients were also determined using DD Solver (Microsoft Excel Version).

Similarity factor

As the name specifies, it stresses on the comparison of closeness of two comparative formulations. Generally similarity factor in the range of 50-100 is acceptable according to US FDA. It efficiently compares dissolution profiles of different formulations (Gulshan *et al*., 2017). F1 and F2 Factor Analysis Software (Microsoft Excel Version) was used.

RESULTS

Different formulations were prepared using guar gum and Eudragit L100-55 in different rations. Formulations F1-F4 had only guar gum with increasing concentration from 8.125 % to 32.5%. Formulations F5-F8 had Eudragit L 100-55 alone in the amount of 8.125% -32.5% while the formulations F9 and F10 contained combination of the two polymers in the amounts 8.125% and 32.5% respectively.

Various physical tests were performed to check the quality of tablets. Table 2 indicates results obtained for each formulation.

In vitro dissolution studies of the prepared matrix tablets were performed in 0.1N HCl for the first 2 hours and pH 6.8 buffer solution up to 12 hours. UV visible spectrophotometer was used to measure absorbance of test formulations and standard. Results of dissolution studies were used to apply kinetic models on the formulations as shown in the table 3 below.

Fig. 4 indicates % drug release from F1 to F4 containing Guar gum in different ratios.

Fig. 5 indicates % drug release of formulations F5 to F8 with Eudragit L 100-55 polymer.

Fig. 6 indicates release pattern of formulations F9 and F10 containing both Guar gum and Eudragit L 100-55.

DISCUSSION

Tablets were prepared by direct compression method. Various physical tests were performed to check the quality of tablets. Hardness of the formulations was found within 8.7-10.7kg/cm^2 that indicated good mechanical resistance of the formulated tablets. Friability was found to be from 0.04% to 0.29%. Weight variation was within ± 0.4% to ±1.58% for all the formulations. All the physical parameters were found to be within official limits (table 2).

In vitro dissolution was also performed on tablets from each formulation. It was observed that release of drug in buffer pH 6.8 was slow as compared to 0.1N HCl, where initial bursting of drug was noted. As the concentration of polymer was increased or the combination of polymers was used, the swelling of the matrix took place and drug release was reduced.

Since natural gums are more cost effective and safer, Guar Gum was used to prepare matrix tablets. Its compaction and flow properties have found to be suitable for direct compression. In formulations F1 to F4, Guar gum was used in the ratios 1:0.5, 1:1, 1:1.5 and 1:2 respectively. All the formulations sustained up to 8 hours. As the concentration of polymer was increased from 8% to 32%, release of drug became slow and sustaining effect was increased (fig. 4).

Table 1: Composition of formulations

S. No.	Formulation	Polymer %		Lactose
1.	F1	Guar Gum	8.125%	75.28%
2.	F2	Guar Gum	16.25%	67.15%
3.	F3	Guar Gum	24.38%	59.03%
4.	F4	Guar Gum	32.5%	50.9%
5.	F5	Eudragit L-100	8.125%	75.28%
6.	F6	Eudragit L-100	16.25%	67.15%
7.	F7	Eudragit L-100	24.38%	59.03%
8.	F8	Eudragit L-100	32.5%	50.9%
9.	F9	Guar Gum + Eudragit L-100	8.125%	75.28%
10.	F10	Guar Gum + Eudragit L-100	32.5%	50.9%

*Drug concentration in all the formulations was 16.25% while the concentration of magnesium stearate and aerosil were 0.25% and 0.1%respectively.

Table 2: Physical parameters of formulations

S. No.	Formulation	Hardness (kg / cm^2)	Friability %	Weight variation %
1.	F1	10.2	0.290	± 1.2 %
2.	F2	10.3	0.193	± 1.58 %
3.	F3	10.3	0.200	± 0.95 %
4.	F4	10.7	0.043	± 0.4 %
5.	F5	10.1	0.147	± 0.9 %
6.	F6	10.7	0.098	± 0.79 %
7.	F7	10.4	0.129	± 0.54 %
8.	F8	8.7	0.146	± 1.2 %
9.	F9	10.6	0.182	± 1.34 %
10.	F10	10.3	0.197	± 1.29 %

Table 3: Kinetic modeling data for formulations F1 to F10

Formulations	Zero order kinetics	First order kinetics	Higuchi model	Korsmeyer Peppas model	
	R^2	R^2	R^2	R^2	n
F1	0.9004	0.8806	0.9593	0.9502	0.5536
F2	0.9042	0.8756	0.9628	0.9563	0.5483
F3	0.9053	0.8676	0.9581	0.9415	0.5344
F4	0.9225	0.8502	0.9561	0.9415	0.5509
F5	0.9079	0.8843	0.9657	0.9664	0.6071
F6	0.9182	0.8787	0.9588	0.9625	0.6558
F7	0.9410	0.8786	0.9834	0.9907	0.6670
F8	0.9548	0.8646	0.9741	0.9906	0.7347
F9	0.9354	0.8833	0.9893	0.9866	0.5376
F10	0.9598	0.8295	0.9867	0.9932	0.6122

Formulations F1 and F2 showed initial burst release from the start of the dissolution while the other two slowly released the drug. After a short time period, a linear release behavior was observed. When matrix swells, a portion of dissolved drug is released and after reaching a constant state of gelling, greater amounts of drug could be released by diffusion.

As shown in table 3, all the formulations from F1 to F4, followed zero order kinetics that indicated that drug release was independent of the concentration. All the formulations followed Higuchi model that indicates drugs were released by the process of diffusion. The value of n from Korsmeyer Peppas model suggested that all the formulations F1, F2, F3 and F4 followed the non-fickian release behavior which means drugs were released by both diffusion and erosion controlled mechanisms.

When comparing low and high concentrations of guar gum, similarity factor comes out to be less than 50 that means concentration change affects the properties of polymer. There is no similarity between the low and high concentration.

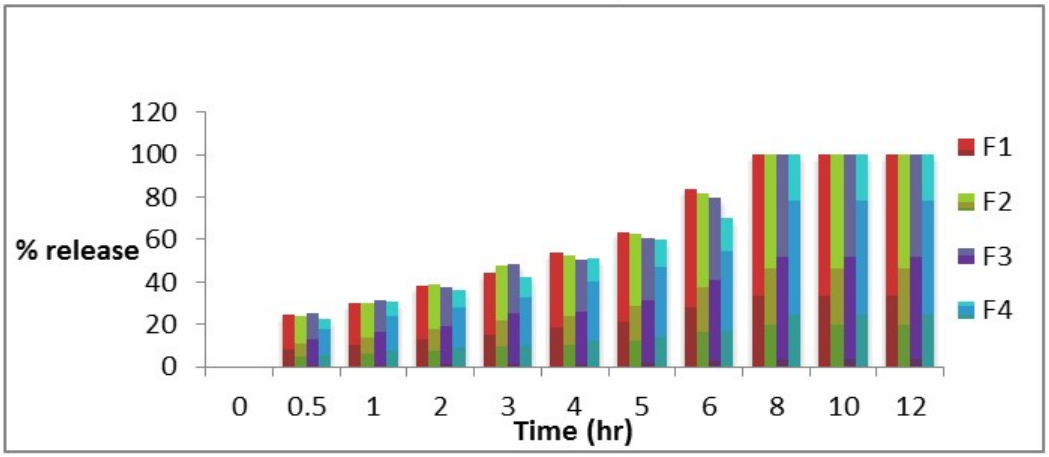

Fig 4: Comparative % drug release of formulations F1 to F4 containing guar gum

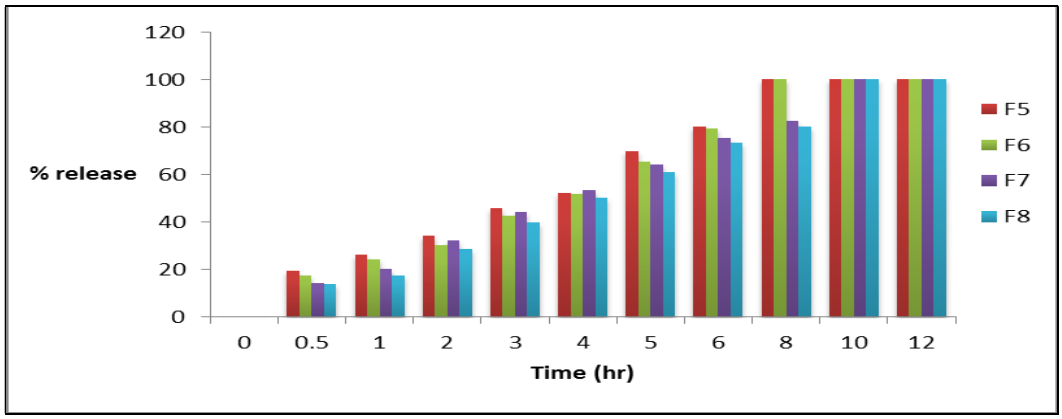

Fig 5: Comparative % drug release of formulations F5 to F8 containing Eudragit L 100-55

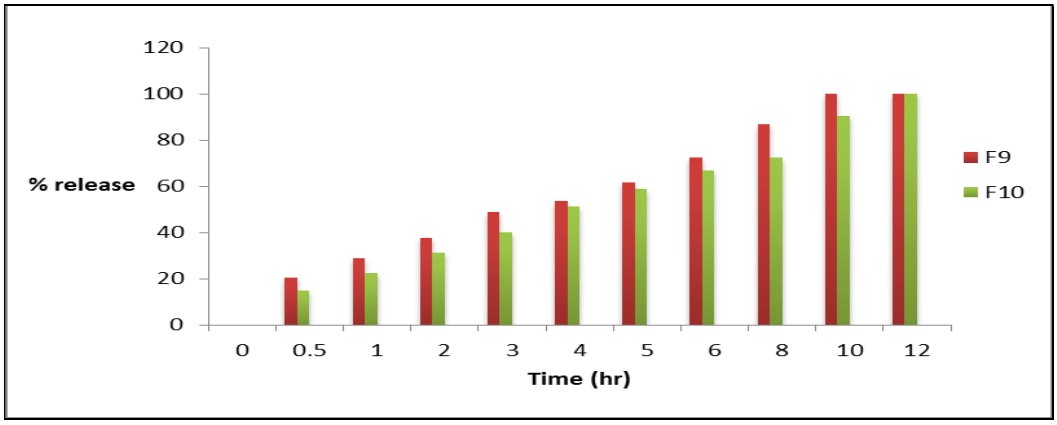

Fig 6: Comparative % drug release of formulations F9 and F10 containing guar gum and Eudragit L 100-55

Formulations F5 to F8 (containing Eudragit L 100-55) showed that drug release was quite slow as compared to formulations F1 to F4. Formulations F5 and F6 were containing 8% and 16% of the polymer concentrations respectively and sustained up to 8 hours while the other two formulations (F7 and F8) sustained up to 10 hours (Fig 5). (Shabbir *et al*., 2017) conducted a similar study for formulation and characterization of curcumin nanoparticles prepared from Eudragit L 100-55 and poly vinyl alcohol as polymer. They used drug and polymer ratios 1:1, 1:2 and 1:3 respectively in different formulations. Their results showed *in vitro* release was sustained for 12hrs. This indicates that synthetic polymer was better than the natural one for slowing down the drug release.

Table 3 indicated that all the formulations followed zero order kinetics as the drug release was independent of the concentration. All the formulations followed Higuchi model that indicates drugs were released by the process of

diffusion. The value of n from Korsmeyer Peppas model suggested the non-fickian release behavior which means the drugs were released by both diffusion and erosion controlled mechanisms.

When comparing low and high concentrations of Eudragit L 100-55 in different formulations, it is seen that similarity factor is 87.3316 which is close to 100 so it is concluded that these formulations are somewhat similar irrespective of the concentration change. With increasing concentration the sustained effect is higher but properties of polymer do not change.

Formulations F9 and F10 (containing Guar Gum and Eudragit L 100-55) showed synergistic effect since combination of polymer was used. Formulation F9 had 8% polymer combination and sustained up to 10 hours while with 32% polymer combination, formulation F10 sustained drug release up to 12 hours. This clearly showed that combination of natural polymer with the synthetic one enhances drug release retarding behaviour than using any of them alone. Fig. 6 indicates % drug release from F9 and F10.

While table 3 shows that both formulations followed zero order kinetics indicating the drug release was independent of the concentration. Also both followed Higuchi model since drugs were released by the process of diffusion. The value of n from Korsmeyer Peppas model suggested that both of them followed the non-fickian release behavior which means the drugs were released by both diffusion and erosion controlled mechanisms.

While comparing low concentrations of both polymers, similarity factor comes out to be 78.155 showing that at low concentration both polymers have same sustained effect irrespective of their chemical nature. At high concentration, no similarity is seen as factor f2 is 47.6397 which is because of dose dumping effect of guar gum at high concentration due to its hydrophilic nature but in case of Eudragit L 100-55, marked sustained effect is seen with increased concentration.

CONCLUSION

From the above drug release profiles, it can be concluded that sustained effect is highly dependent on the nature as well as the concentration of polymers. Guar gum alone cannot efficiently control drug release. Similarly, Eudragit L 100-55 alone produces slower release of drug compared to Guar Gum but the combination of two polymers has better sustained release effects. Eudragit L 100-55 when used in higher concentration retarded the release of drug proficiently so, it should be further investigated for such type of preparations where sustained effect of drugs is desired.

REFERENCES

Agarwal G and Kaushik A (2012). *Pharmaceutical Technology,* CBS Publishers and Distributors Pvt. Ltd., India.

BP (2013). *British Pharmacopoeia,* British Pharmacopoeia Commission Office, London.

Brunton LL, Chabner BA and Knollmann BC (2011). *Goodman And Gilman's The Pharmacological Basis Of Therapeutics,* China, The McGraw-Hill Companies, Inc.

Chime S, Onunkwo G and Onyishi I (2013). Kinetics And Mechanisms Of Drug Release From Swellable And Non Swellable Matrices: A Review. *Res. J. Pharm. Biol. Chem. Sci.,* **4**(2): 97-103.

Chowdary P, Sravani T and Basheeruddin M (2017). Formulation and evaluation of sustained release tablets of nateglinide by using natural polymers. *International Journal of Advances In Pharmaceutical Sciences,* **9**(1): 8-13.

Dash S, Murthy PN, Nath L and Chowdhury P (2010). Kinetic modeling on drug release from controlled drug delivery systems. *Acta Pol. Pharm.,* **67**(3): 217-223.

Derayea SM, Badr EL, Din KM and Mohammed FF (2017). Selective spectrofluorimetric method for determination of lisinopril in pharmaceutical preparations and in presence of hydrochlorothiazide: application to content uniformity testing. *Luminescence*. **32**(8):1482-1487.

DINDA SC (2011). Advances in Pharmaceutical Technology, India, Pharmamed Press.

Gulshan R, Irfan M, Zahoor AF, Arshad MS, Khan NI, Hussain A, Abbas N and Mohsin N-U-A (2017). Effect of formulation and process parameters on drug release from controlled release matrix tablets of terbulatine sulphate. *Latin American Journal of Pharmacy,* **36**(2): 314-325.

Ijaz H, Sethi A, Qureshi J, Anwar N, Ahmad M and Chaudry F (2013). Formulation and *in vitro* evaluation of oral fast disintegrating tablet of lisinopril maleate. *International Journal of Advances In Pharmaceutical Research,* **4**: 2601-2608.

Jagdale SC, Suryawanshi VM, Pandya SV, Kuchekar BS and Chabukswar AR (2014). Development of press-coated, floating-pulsatile drug delivery of lisinopril. *Sci. Pharm.,* **82**(2): 423-440.

Kannan K, Manikandan M, Periyasamy G and Manavalan R (2012). Design, development and evaluation of metoprolol succinate and hydrochlorothiazide bilayer tablets. *J. Pharm. Sci. And Res.,* **4**: 1827-1835.

Kasid I, Saleem M, Parveen R, Parveen N and Sheikh A A (2013). Development of bilayer tablets of lisinopril and gliclazide: *in vitro* and *in vivo* evaluation. *scholars research library. Der Pharmacia Lettre,* **5**: 54-62.

Nagendrakumar D, Shirsand S, Keshavshetti G and Biradar S (2013). Design and evaluation of lisinopril

buccal tablets. *International Journal of Universal Pharmacy and Bio Sciences,* **2**: 387-400.

Patil BS, Motagi AM, Kulkarni U, Hariprasanna RC and Patil S (2012). Development and evaluation of time controlled pulsatile release lisinopril tablets. *Journal of Pharaceutical Science and Bioscientific Research,* **2**: 30-35.

Ratilal DA, Gaikward PD, Banker VH and Pawar SP (2011). A review on sustained release technology. *International Journal of Research And Pharmaceutical Science,* **2**: 1701-1708.

Senkardes S, Ozaydın T, Ugurlu T and Kucukguzel SG (2017). Development and validation of a reversed-phase hplc method for the determination of lisinopril and gliclazide in pharmaceuticals. *Marmara Pharmaceutical Journal,* **21**: 338-344.

Shabbir M, Fazli AR, Ali S, Raza M, Sharif A, Akhtar MF, Ahmed S, Peerzada S, Younas N and Manzoor I (2017). Effect of hydrophilic and hydrophobic polymer on i*n vitro* dissolution and permeation of bisoprolol fumarate through transdermal patch. *Acta Poloniae Pharmaceutica,* **74**: 187-197.

Shah JV, Shah PA, Sanyal M and Shrivastav PS (2017). Simultaneous quantification of amiloride and hydrochlorothiazide in human plasma by liquid chromatography-tandem mass spectrometry. *J. Pharm. Anal.,* 7(5): 288-296.

Singhvi G and Singh M (2011). Review: *In vitro* drug release characterization models. *Int. J. Pharm. Stud. Res.,* **2**: 77-84.

Viswanadhan PV, Padole A, Abraham A and Mathew S T (2012). Buccal tablets of lisinopril by direct compression method for buccal drug delivery. *International Research Journal of Pharmaceuticals,* **2**: 30-38.