Australian Journal of Science and Technology

ISSN Number (2208-6404)
Volume 6; Issue 1; March 2022

Original Article

Formulation and evaluation tablets of perindopril erbumine-layered double hydroxides prepared by direct compression method

Samer Hasan Hussein-Al-Ali[1,2]*, Rasha Khaled Ali Abuthawabeh[1,3], Nour Sadeq Ali, Hmaidan[1], Hanadi Abdel Ibrahim Efseseh[1]

[1]Department of Basic Pharmaceutical Sciences, Faculty of Pharmacy, Isra University, Amman, Jordan, [2]Department of Chemistry, Faculty of Science, Isra University, Amman, Jordan, [3]Applied Pharmaceutical Sciences, Faculty of Pharmacy, Amman, Jordan

ABSTRACT

The aim of this work is to prepare the tablet of perindopril erbumine (PPE)-layered double hydroxide nanocomposites (PPE-LDHs) using direct compression method. The tablet consists from starch as binder, stearate as lubricants and aerosol, and talc as glidants agent. The PPE-LDHs tablets were evaluated for different properties, such as drug content, thickness, friability, hardness, diameter, weight variation, and release study. The data indicated that all the parameters comply with the official standards. From the release study for seven patches, all exhibit long release and reached up to 1500 min, which support the extended release property. The PPE-LDHs tablets show better sustained release property when compared with powder PPE-LDHs which published in 2012.

Keywords: Direct compression method, layered double hydroxide, perindopril erbumine, sustained release, tablet

Submitted: 01-01-2022, **Accepted:** 17-02-2022, **Published:** 30-03-2022

INTRODUCTION

The immediate release formulations, such as tablets and capsules, are delivered the drug to active set to obtain rapid and complete systemic absorption and onset of the pharmacodynamic effects.[1] Therefore, the patient takes his dose at several times to maintain the drug concentration at constant level in plasma.

In the case of prodrugs and immediate release, the pharmacodynamic activity procures slowly due to conversion from prodrug to active drug through hepatic or chemical hydrolysis or by intestinal metabolism.[1] In addition, the oral lipid drug has slow dissolution and non-selective absorption through the GI tract, which leads to delay in onset time.

The term sustained release is a system that designed to achieve a prolonged therapeutic blood of the drug through continuous release after administration of a single dose. Therefore, plasma concentrations are kept at a therapeutic level for a long time.[2]

Layered double hydroxides (LDHs) are class of positively charged brucite-like nanolayers with an interlayer spacing containing water molecules and anions. The most structure of LDHs contain both di- and tri-metal cations with general formula as: $[M^{2+}_{1-x}M^{3+}_{x}(OH)_2][A^{n-}]_{x/n}\cdot zH_2O$, where M^{2+} cations such as Ni^{2+}, Zn^{2+}, or Mg^{2+}, and M^{3+} cations such as Fe^{3+}, Al^{3+}, Mn^{3+}, or Ga^{3+}, A^{n-} is an organic or inorganic anion such as RCO_2^-, CO_3^{2-}, Cl^-, SO_4^{2-}, or NO_3^-, and x is the mole fraction of M^{3+}.[3-5]

The most attractive property of LDHs as drug carriers was biocompatibility and their low toxicity.

Many studies of the M^{2+}-M^{3+}-LDHs show low toxicity properties. For example, MgAl-LDHs and ZnAl-LDHs are most nanolayers used as drug carrier with low toxic properties.[6] In addition, LDHs within the size between 100 and 200 nm show low cytotoxicity properties in terms of inflammation, membrane damage response, and cell proliferation.[7] Furthermore, LDHs show enhance in the internalization of

Address for correspondence: Samer Hasan Hussein-Al-Ali, Faculty of Pharmacy, Isra University, Amman, Jordan. E-mail: samer.alali@iu.edu.jo/sameralali72@yahoo.com

the drug to the specific cell without any side effects.[8] 5-Fu-LDHs exhibit sustained release property and increased 5-Fu accumulation in target tumor tissue.[9]

Perindopril erbumine (PPE) is the combination of tert-butylamine with perindopril. By hydrolysis, PPE is converted to its active form perindoprilat, inhibiting angiotensin-converting enzyme and convert angiotensin I to angiotensin II.

Many early PPE nanoparticles were studied, for example, the PPe was loaded on the PEG-MNPs for biomedical applications.[10] In addition, PPE was combined with chitosan nanoparticles as a drug delivery system.[11] Furthermore, PPE was intercalated into Zn/Al-NO_3-LDHs. The release of PPE from the nanocomposite was completed with 300 min.[12]

According to our PPE nanocomposites, the aim of this study was to develop a pharmaceutically tablet of PPE-LDHs and quality improved formulation. To achieve this goal, various formulations were taken and evaluated the release property.

MATERIALS

PPE with chemical formula $C_{23}H_{43}N_3O_5$, molecular weight 441.6 g/mole, and 99.8% purity was purchased from CCM Duopharma (Berhad, Malaysia). Starch and sodium stearate were purchased from A2 Chem for chemicals. Aerosil (0.2%) and talc (1%) were purchased from S & C Chemical Supplico Chemicals.

METHODS

Preparation of PPE-LDHs Nanocomposite

Incorporation of PPE into inner space of LDHs was performed using the coprecipitation method. The $Zn(NO_3)_2.6H_2O$ (4 molar) and $Al(NO_3)_3.9H_2O$ (1 molar) were dissolved in 150 ml of deionized water. The PPE was added dropwise to mixture of LDHs in the presence of nitrogen gas with constant stirring. The pH was kept at 7 using 0.5 molar NaOH solution. The appearance of a white gelatinous precipitate indicated the formation of PPE-LDHs nanocomposite. The PPE-LDHs were kept into oil bath for further 24 h. The nanocomposite was then centrifuged, washed with distilled water to remove nitrate and excess PPE, and then oven-dried.

Determination of λ_{max} for PPE

The drug PPE was dissolved in distilled water to obtain 100 ppm solutions. The maximum absorbance (λ_{max}) was determined in the range 200–400 nm using double-beam UV-VIS Spectrophotometer.

Preparation of Calibration Curve for PPE

Approximately 50 mg of PPE was added to 100 ml distilled water. Different concentrations of PPE solutions were prepared (0.5, 1, 2, 4, 8, 16, and 32 ppm), and then, the absorbance was measured using spectrophotometrically at 215 nm wavelength.

Preparation of Tablets Formulations

The composition tablet of PPE-LDHs is prepared according to Table 1 using direct compression method. All the excipients and PPE-LDHs were mixed in mortar and then compressed using hydraulic press (Erweka, Type EKO, Germany) to produce the tablets with the compression force of 1 ton/cm^2.

Quality Control of Tablets

Uniformity of weight for tablets

The uniformity of weight test was performed by taken randomly 20 PPE-LDHs tablets. The procedure described in USP 30 NF 25.[13] A 20 PPE-LDHs tablets are weighed and then the average weight was determined.[14] The deviation of individual weight from the average weight should not exceed the limits which suggested from USP 30 NF 25.[13] The deviation in average weight was calculated using Equation 1.

$$\text{Deviation of weight} = \frac{\text{Net weight of tablets- average net weight of tablets}}{\text{average net weight of tablets}} \times 100\% \quad \text{Eq.1}$$

Hardness

Hardness of all batches was measured using Digital Force Gauge (Erweka, TBH-30, UK). The test was repeated in triplicate for all batches.[13,15]

Thickness

The thickness of the PPE-LDHs tablets was measured using Vernier caliper (Mitutoyo Dial Thickness Gauge, Mitutoyo, Japan). The thickness was expressed as mean values.[16,17]

Friability test

Tablets friability were determined using Erweka, Type TAR-20, UK. About 10s of tablets were accurately weighted, placed in the friabulator, and rotated at 25 rpm. The percentage weight lost was determined using Equation 2.[18]

$$\%\ \text{Loss} = \frac{\text{weight before- weight after}}{\text{weight before}} \times 100\% \quad \text{Eq. 2}$$

Table 1: Composition of PPE-LDHs tablet

Formula	F1	F2	F3	F4	F5	F6	F7
PPE-LDHs	132	132	132	132	132	132	132
Aerosol (mg)	0.4	0.4	0.4	0.4	0.4	0.4	0.4
Starch (mg)	65.6	65.1	63.6	62.1	60.6	58.1	55.6
Na-stearate (mg)	-	0.5	2	3.5	5	7.5	10
Talc (mg)	2	2	2	2	2	2	2
Weight/tab	200	200	200	200	200	200	200

Diameter Test

Tablet diameter can be measured by a Vernier caliper using 5–10 tab.

Determination of PPE Content in PPE-LDHs Tablets

Three tablets from each batch were selected randomly and transferred to a 100 ml volumetric flask filled with 0.1 N HCl and sonicated 3 h. The diluted samples were analyzed using UV spectrophotometrically (Shimadzu UV-1601) at λ_{max} 215 nm wavelength.[11,12,19,20] The PPE content of the each sample was estimated from the calibration standard curve.[21,22]

In vitro PPE Release Study

Known amount of formulations was added to 900 ml of PBS at pH 7.4. Around 3 ml of each formulation was withdrawn after specified time interval. Collected samples were analyzed using UV spectrophotometrically (Shimadzu UV-1601) at λmax 215 nm wavelength, and cumulative percent drug release was calculated using Equation 3.

$$\% \text{ Release} = \frac{\text{Concentration of PPE at time t (ppm)}}{\text{Concentration of PPF in each tablet (ppm)}} X100 \quad \text{Eq.3}$$

RESULTS AND DISCUSSION

Lambda Max Determination for PPE

Figure 1 shows the wavelength of PPE corresponding to maximum absorbance (λ_{max}). The result shows that the wavelength value was 215 nm.

Calibration Curve of PPE

Figure 2 shows the calibration curve of PPE. The data showed a good linear relationship over the concentration range, 0.5–32 ppm, with equation Y = 0.02518X+0.01795. Correlation coefficient (R^2) was found to be 0.9937.

Evaluation Parameters of PPE

Thickness of tablets

The thickness property of tablets is not listed in the pharmacopoeia standards, but it is major important to be measured to control the quality for tablet. The uniformity thickness is important for different reasons: First, to reproduce tablets identical in its appearance and second in counting tablets using filling equipment. Figure 3 and Table 2 show the experiment for test the uniformity of PPE tablets in the aspect of thickness. Based on own result, the mean thickness of 10 tablets is 2.299 mm, within the range of 2.09–2.88 mm. The small value of difference in the thickness indicates that the PPE-LDHs tablets are uniform in their thickness.[23] Thickness can be change in same patch due to difference in speed during tablet compression, pressure applied, and density of granulation.

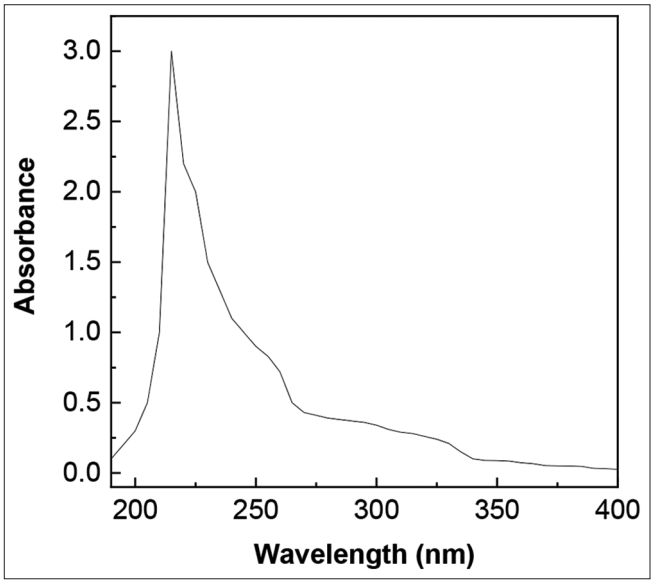

Figure 1: UV spectrum of PPE (λ_{max} determination)

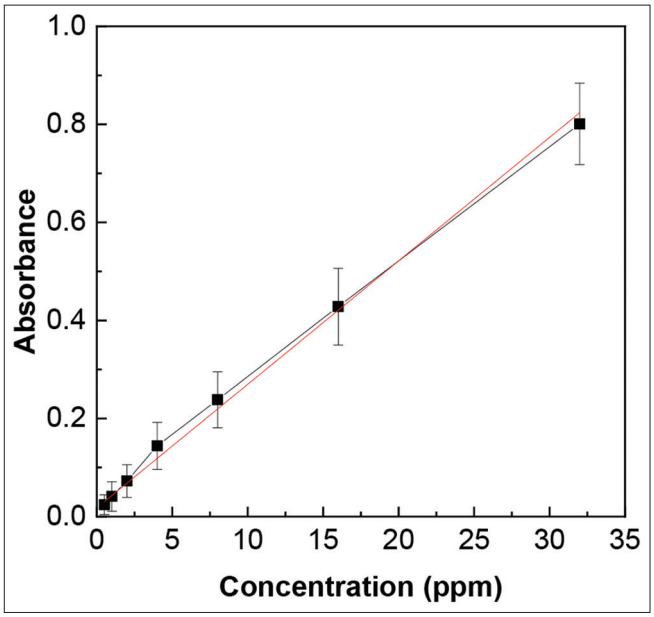

Figure 2: Calibration curve of PPE

Diameter of tablets

The thickness property of the tablets differs from the diameter that the latter is included in the pharmacopeia standard assessment.[24] The uniformity in diameter of any tablets is very necessary to save patient from any confuse with different size of the tablets and increase the patient compliance. In addition, various sizes of the tablets may lead to make confuse to the patient on the amount of active ingredient in the tablets. From

Table 2: Evaluation parameters of PPE in pharmaceutical formulation by direct compressed formulations

Formulations	Evaluation parameters					
	Diameter (mm)	Hardness (Newtons)	Thickness (mm)	Weight variation (%)	Friability test (%)	Drug content (%)
F1	7.97	45	2.88	2.1	0.347	98.3
F2	7.99	48	2.25	1.9	0.973	99.4
F3	7.97	47	2.09	2.3	0.225	98.9
F4	7.92	56	2.18	2.0	0.564	98.0
F5	7.98	59	2.20	1.3	0.853	99.1
F6	7.96	57	2.28	1.6	0.958	95.2
F7	7.91	60	2.21	1.9	0.462	97.4

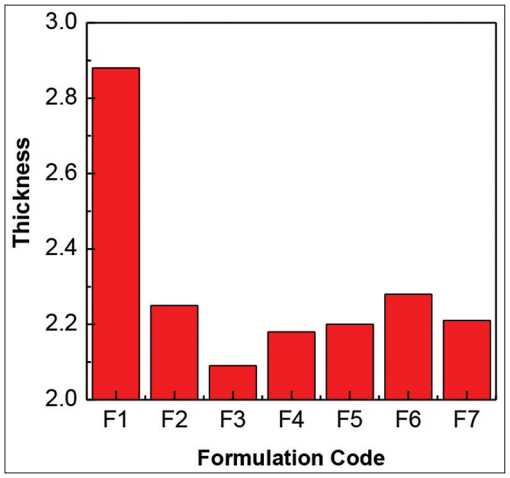

Figure 3: Effect of composition of PPE-LDHs nanocomposites on thickness of tablets

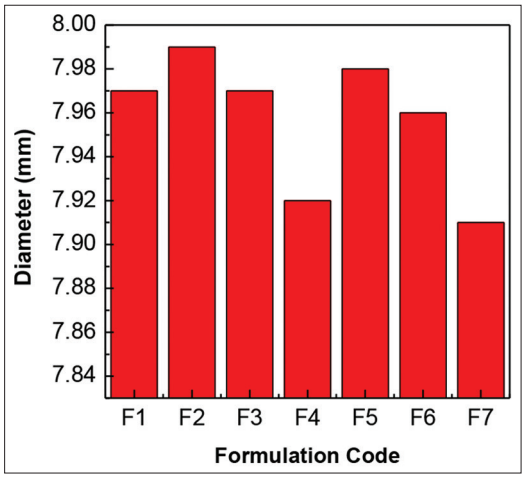

Figure 4: Effect of composition of PPE-LDHs nanocomposites on diameter of tablets

the pharmacopoeia, the deviation in the mean diameter should not exceed ± 3% for diameter of 12.5 mm or more and ± 5% for tablets with diameter of less than 12.5.[24] From our results at Figure 4 and Table 2, the range of the diameter of the tablets lies between 7.91 mm and 7.99 mm. In addition, the deviation of diameter does not exceed ±5%, this result shows that the formulation of PE-LDHs nanocomposite really complies with the pharmacopeia standard.

Hardness of tablets

The hardness property of the tables also not listed in pharmacopeia standard, it is an important property to evaluate the uniformity of hardness of the any tablets. Too hard tablets will not disintegrate in the suitable period of time and therefore will fail the dissolution test. In addition, too soft tablet will be will be unable to resist handling during shipping , operations coating, and packaging. The hardness term can define as crushing strength, the minimum crushing strength is about 4 kg/m^2, which is suitable for tablets. The hardness of tablets from all batches was found to be in the range of 45–60 Newton's [Figure 5 and Table 2], which equal to 4.5–6.0 kg.[25]

Weight variation of tablets

The weight of a tablet is determined by quantity of fill in the die of a tablet press, it measures of contents by the estimation of contents based on weight. Weight variation of tablets used to measure content uniformity of the tablet. Since our average weight is 202.2 mg, the deviation of net weight should not exceed to ±7.5%. From Figure 6 and Table 2, the weight deviation for tablet from F1 toF7 was 2.1, 1.9, 2.3, 2.0, 1.3, 1.6, and 1.9, respectively, indicates that the tablets passed in the test of weight uniformity.[26]

Friability of tablets

Friability test can be defined as the % weight loss of powder from the surface of the tablets by the mechanical action. It is simulated to weight loss due to transportation of drug tables. If the test obvious broken tablets, cleaved, or cracked, the tablet fails the test. A maximum mean weight loss from this test should not more than 1.0%.[27] From Figure 7 and Table 2, the weight loss deviation for the seven patch was 0.626%, which is <1%, indicates tablets passed in the friability test.

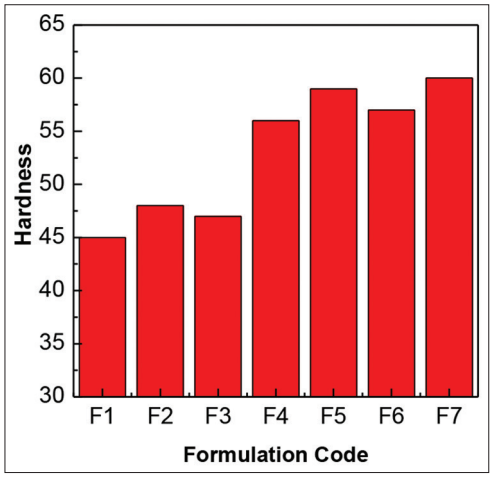

Figure 5: Effect of composition of PPE-LDHs nanocomposites on hardness of tablets

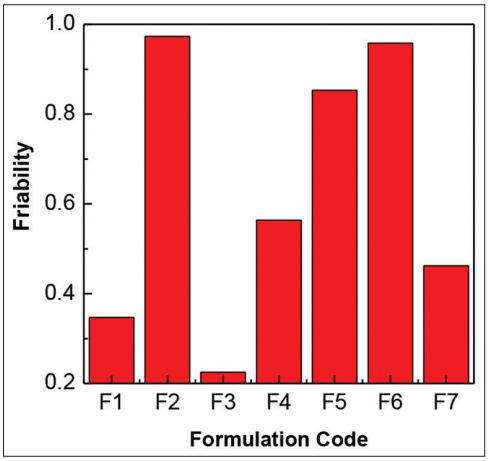

Figure 7: Effect of composition of PPE-LDHs nanocomposites on friability of tablets

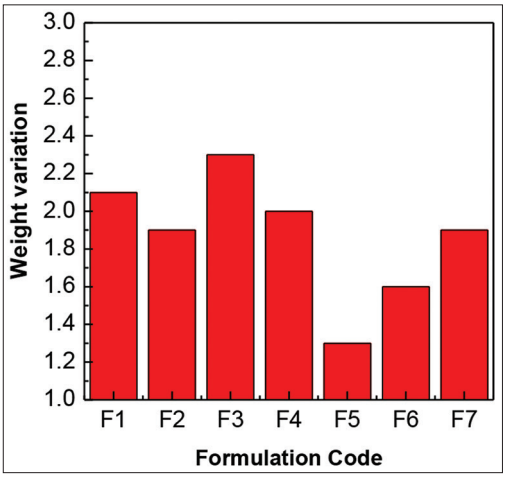

Figure 6: Effect of composition of PPE-LDHs nanocomposites on weight variation of tablets

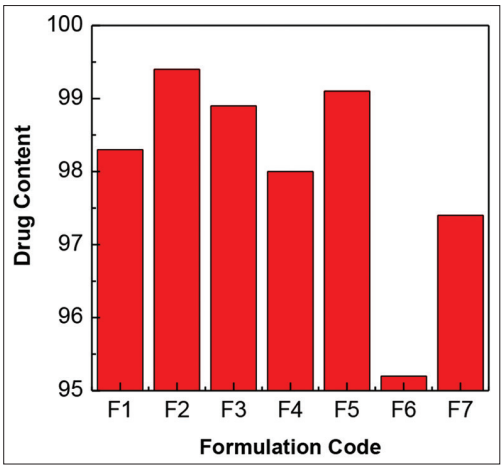

Figure 8: Effect of composition of PPE-LDHs nanocomposites on drug content of tablets

Drug content in tablets

The percentage drug content for different patch tablets formulations was varied from 95.2 to 99.4 indicating the uniformity in drug content, as shown in Table 2 and Figure 8.

Release Study of PPE from PPE-LDHs Nanocomposites

The PPE release profile from the PE-LDHs tablets was studied *in vitro* using PBS at pH 7.4. From Figure 9 and 10, the formulations F2, F5, F6, and F7 have shown fast release of about 80%, 70%, 62%, and 63% at 200 min, respectively. The formulations F1, F3, and F4 have shown slow release with 35%, 37%, and 22% at 200 min, respectively . In addition, the formulations shows very slow release to completed within 1800 min. It is slower release comparing to last our work.[12] The order of PPE release was found to be F2>F5>F4>F7>F6>F3>F1. The release data of F1 and F4 formulations fitted well into the

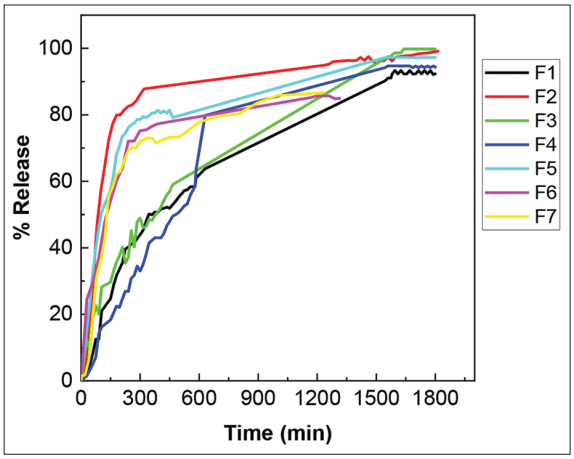

Figure 9: *In vitro* release behaviors of PPE from PPE-LDHs nanocomposites in the 7.4 PBS buffer

first-order equation with correlation coefficient values were 0.9930 and 0.9865, respectively, while F2, F5, and F6 follow

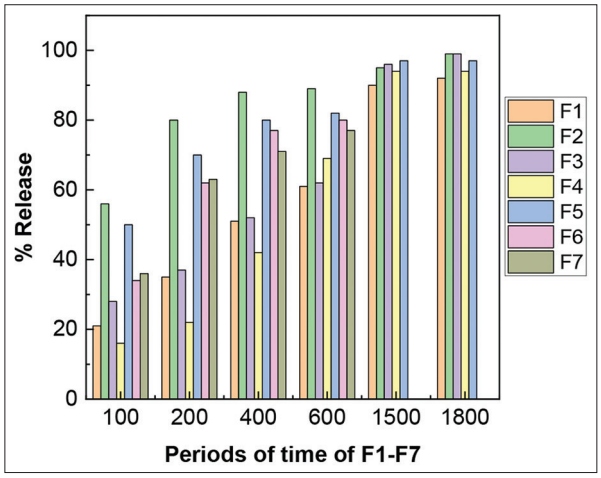

Figure 10: Release behaviors of PPE at fixed period time

second-order release with correlation coefficient values 0.9595, 0.9854, and 0.9984, respectively. The F3 and F7 were fitted by Higuchi model with correlation coefficient values 0.9922 and 0.8828, respectively.

CONCLUSION

In this work, it was pointed the promising use tablet of PPE-LDHs as drug delivery system. These tablets were prepared by direct compression method PPE-LDHs with binder, lubricants, and Glidants agents. The results also suggested the sustained release properties for tablets.

DECLARATION OF CONFLICTING INTEREST

The authors report no conflicts of interest in this work.

FUNDING ACKNOWLEDGMENT

The author would like to thank the Faculty of Pharmacy at Isra University provided funding for this research.

REFERENCES

1. Rathbone MJ, Hadgraft J, Roberts MS. Modified-release Drug Delivery Technology. Boca Raton, Florida: CRC Press; 2002.
2. Chien YW. Novel Drug Delivery Systems-Drugs and the Pharmaceutical Sciences. Vol. 3. New York: Marcel Dekker Inc.; 2006.
3. dos Santos GE, dos Santos Lins PV, Oliveira MT, da Silva EO, Anastopoulos I, Erto A, *et al*. Layered double hydroxides/biochar composites as adsorbents for water remediation applications: Recent trends and perspectives. J Clean Prod 2021;284:124755.
4. Gu Z, Atherton JJ, Xu ZP. Hierarchical layered double hydroxide nanocomposites: Structure, synthesis and applications. Chem Commun 2015;51:3024-36.
5. Scarpellini D, Falconi C, Gaudio P, Mattocia A, Medaglia PG, Orsini A, *et al*. Morphology of Zn/Al layered double hydroxide nanosheets grown onto aluminum thin films. Microelectron Eng 2014;126:129-33.
6. Tarnawski AS, Tomikawa M, Ohta M, Sarfeh IJ. Antacid talcid activates in gastric mucosa genes encoding for EGF and its receptor. The molecular basis for its ulcer healing action. J Physiol Paris 2000;94:93-8.
7. Choi SJ, Oh JM, Choy JH. Safety aspect of inorganic layered nanoparticles: Size-dependency *in vitro* and *in vivo*. J Nanosci Nanotechnol 2008;8:5297-301.
8. Oh JM, Biswick TT, Choy JH. Layered nanomaterials for green materials. J Mater Chem 2009;19:2553-63.
9. Choi SJ, Oh JM, Choy JH. Biocompatible nanoparticles intercalated with anticancer drug for target delivery: Pharmacokinetic and biodistribution study. J Nanosci Nanotechnol 2010;10:2913-6.
10. Dorniani D, Kura AU, Hussein MZ, Fakurazi S, Shaari AH, Ahmad Z. Controlled-release formulation of perindopril erbumine loaded PEG-coated magnetite nanoparticles for biomedical applications. J Mater Chem 2014;49:8487-97.
11. Hussein-Al-Ali SH, Kura A, Hussein MZ, Fakuarzi S. Preparation of chitosan nanoparticles as a drug delivery system for perindopril erbumine. Polym Compos 2018;39:544-52.
12. Al Ali SH, Al-Qubaisi M, Hussein MZ, Ismail M, Zainal Z, Hakim MN. Controlled release and angiotensin-converting enzyme inhibition properties of an antihypertensive drug based on a perindopril erbumine-layered double hydroxide nanocomposite. Int J Nanomed 2012;7:2129-41.
13. Pharmacopoeia US. The National Formulary (USP 30-NF 25), the Official Compendium of Standards. Rockville, MD: United State Pharmacopoeial Convention; 2007.
14. Vidyadhara S, Rao PR, Prasad J. Development and *in vitro* kinetics of propranolol hydrochloride controlled release matrix tablets. Indian Pharm 2006;5:66-70.
15. Ei-Arini SK, Leuenberger H. Modelling of drug release from polymer matrices: Effect of drug loading. Int J Pharm 1995;121:141-8.
16. Schmidt RH, Haupt K. Molecularly imprinted polymer films with binding properties enhanced by the reaction-induced phase separation of a sacrificial polymeric porogen. Chem Mater 2005;17:1007-16.
17. Schiermeier S, Schmidt PC. Fast dispersible ibuprofen tablets. Eur J Pharm Sci 2002;15:295-305.
18. Khan R, Ashraf MS, Afzal M, Kazmi I, Jahangir MA, Singh R, *et al*. Formulation and evaluation of sustained release matrix tablet of rabeprazole using wet granulation technique. J Pharm Bioallied Sci 2014;6:180.
19. Al Ali SH, Al-Qubaisi M, Hussein MZ, Ismail M, Zainal Z, Hakim MN. Comparative study of Mg/Al-and Zn/Al-layered double hydroxide-perindopril erbumine nanocomposites for inhibition of angiotensin-converting enzyme. Int J Nanomed 2012;7:4251.
20. Katewongsa P, Phaechamud T. Cetirizine dihydrochloride tablets

comprising two different lubricants with highly loaded colloidal silicon dioxide. J Met Mater Miner 2012;22:13-8.
21. Reddy KR, Mutalik S, Reddy S. Once-daily sustained-release matrix tablets of nicorandil: Formulation and *in vitro* evaluation. AAPS PharmSciTech 2003;4:480-8.
22. Krishnaiah Y, Krishnaiah YS, Satyanarayana S. A study on the *in vitro* evaluation of guar gum as a carrier for oral controlled drug delivery. Saudi Pharm J 2001;9:91-8.
23. Koirala S, Nepal P, Ghimire G, Basnet R, Rawat I, Dahal A, *et al*. Formulation and evaluation of mucoadhesive buccal tablets of aceclofenac. Heliyon 2021;7:e06439.
24. Karnick C. Pharmacopoeial Standards of Herbal Plants. Vol. 1. New Delhi: Sri Satguru Publications; 1994.
25. Çelik M. Pharmaceutical Powder Compaction Technology. Boca Raton, Florida: CRC Press; 2016.
26. Yoshida I, Sakai Y. The applications of the content uniformity test and the weight variation test on process validation tests of multiple ingredient preparations. Chem Pharm Bull 1999;47:678-83.
27. Gordon MS. Process considerations in reducing tablet friability and their effect on *in vitro* dissolution. Drug Dev Ind Pharm 1994;20:11-29.