ORIGINAL ARTICLE

LINAGLIPTIN AND GLICLAZIDE DI-LOADED EXTENDED-RELEASE NANOPARTICLES: FORMULATION AND EVALUATION

DOI: 10.36740/WLek202109212

Firas Aziz Rahi[1], Muath Sheet Mohammed Ameen[2], Mohammed Shamil Fayyadh[1]
[1] AL-TURATH UNIVERSITY COLLEGE, BAGHDAD, IRAQ
[2]PHARMACY DEPARTMENT, COLLEGE OF PHARMACY, KNOWLEDGE UNIVERSITY, ERBIL, KURDISTAN REGION, IRAQ

ABSTRACT

The aim: This work aimed to formulate gliclazide and linagliptin extended-release nanoparticles.

Materials and methods: A HPLC method was developed and validated to determine gliclazide and linagliptin at the same time without interference. The nanoparticles were prepared by emulsion solvent evaporation using two polymers, namely hydroxypropyl methylcellulose (HPMC) 4000 cps and xanthan gum.

Results: Nanoparticles prepared were characterized for drug contents, production yield and entrapment efficiency, zeta potential, particle size, morphology by transmission electronic microscopy (TEM) and *in-vitro* release rate. The formulae GLH1, GLX1 and GHX1 showed release of linagliptin more than 75% after 8 hrs. While the only formula among the three (GHX1) showed release of gliclazide more than 80% after 8 h. So, the formula GHX1 showed acceptable release of more than 80% of both gliclazide and linagliptin after 8 h.

Conclusions: The formula GHX1 which containing (0.5:1 xanthan gum: drugs) was the best nanoparticles formula which released more than 80% of both drugs after 8 h and could achieve good extended release over 24 h.

KEY WORDS: linagliptin, gliclazide, extended release, nanoencapsulation, HPLC method

Wiad Lek. 2021;74(9 p.II):2315-2322

INTRODUCTION

Gliclazide is used to control blood glucose in patients with type II diabetes mellitus which is known as non-insulin-dependent diabetes. Gliclazide is used when diet and exercise are not enough to control blood glucose. Gliclazide can be used alone or together with insulin or other medicines for treating diabetes [1]. Chemically Gliclazide is described as [1-(3-azabicyclo (3,3,0) oct- 3-yl)-3-p-tolylsulfonylurea]. Gliclazide is comparatively insoluble in water. Linagliptin is an oral antidiabetic drug used in the treatment of type II diabetes mellitus which inhibits the enzyme dipeptidyl peptidase-4 (DPP-4) [2, 3]. Linagliptin belongs to BCS class-III drug i.e., it has high solubility and low permeability [4],

Most patients with type II diabetes mellitus use combinations of antidiabetic drugs to control their blood sugar to the normal level. There is no available marketed product including gliclazide and linagliptin combination. However, there is linagliptin metformin combination extended release as in Jentadueto XR. In the USA, linagliptin/metformin SPC is available in three different dosages approved for twice-a-day use: 2.5/500 mg, 2.5/850 mg, and 2.5/1000 mg [5]. In Europe, two approved doses are available for twice-a-day use: 2.5/850 mg and 2.5/1000 mg [5].

In this research, gliclazide was prepared in combination with linagliptin which is water soluble drug [6] while gliclazide is a poorly soluble drug in extended-release nanoparticles dosage form using two polymers using solvent evaporation method to provide the concentration 60/2.5mg. Among nine formulae, a formula GHX1 exhibited good nanoparticles characteristics and released concerning gliclazide and linagliptin.

THE AIM

This work aimed to formulate gliclazide and linagliptin extended-release nanoparticles.

MATERIALS AND METHODS

MATERIALS

Gliclazide, purchased from CAD Middle East, India. Linagliptin purchased from Lee Pharma, India. HPMC (4000 cps), Dow, France. Acetone, Merck, Germany. dimethylamine for HPLC; E. Merck, Darmstadt, Germany. Hydrochloric acid, sodium hydroxide pellets, formic acid, potassium, Hexane; Schuarlo, Spain. Highly pure water was prepared by using a Milli-Q purification system.

DEVELOPMENT OF HPLC METHOD

The separation was achieved using a Luna C18 (5 µm, 15 cm×4.6 mm) column, Waters HPLC apparatus with pump. Linagliptin and gliclazide were detected at 270 nm which was determined by a photodiode array detector. The injection volume was 20 µl and a mobile phase A consisting

of 2 ml diethylamine in 1000 ml water, pH was adjusted to 3 using formic acid and mobile phase B was acetonitrile, the temperature was 40°C, flow-rate was a gradient of 1.0 ml/ min as Table I.

NANOPARTICLES PREPARATION

600 mg of gliclazide and 50 mg linagliptin were dissolved in 25ml acetone and sonicated till a clear gliclazide linagliptin (linaglic) solution was formed. Different ratios of polymers; HPMC (4000 cps) and xanthan gum were dissolved in 50ml water according to Table II.

Linaglic solution was added dropwise into 50 ml of the dissolved polymer with continuous mixing by homogenizer at 3000 rpm up to 15 min. 1 g of tween 80 was added to 120 ml of hexane and stirred, then added to the polymer(s) loaded with drugs solution dropwise with continuous stirring for 2h.

The obtained dispersion was centrifuged at 16,000 rpm for 20 min. The obtained particles were washed with 10 ml acetone, 10 ml ethanol, and finally with 10 ml water. 2 ml of 10% mannitol w/v was added as cryoprotectant to the washed particles. The prepared particles were frozen at -80°C and lyophilized for 48 h. The lyophilized particles were stored in a refrigerator for further studies.

CHARACTERIZATION OF LOADED NANOPARTICLES

DRUG LOADING, ENTRAPMENT EFFICIENCY OF NANOPARTICLES DRUG ENTRAPMENT EFFICIENCY OF NANOPARTICLES

The drug entrapment efficiency of the nanoparticle formulations was determined indirectly by sedimentation of nanoparticles, employing ultracentrifugation followed by the analysis of unentrapped drugs in the supernatant. The difference between the amount of drug added initially in the formulation and the unentrapped drug found in the supernatant gives the amount of drug entrapped in the formulation. 100 mg of nanoparticle was accurately weighed, dissolved in 65 ml of phosphate buffer (pH 6.8), centrifuged at 15000 rpm for 30 min, completed to the volume of 100ml with acetonitrile and further sonicated for 10 min in sonicator bath. Two milliliters of the supernatant were transferred, filtered through 0.2µm filter and percent of dissolved drugs were determined by the developed HPLC method. The drug contents, production yield, and entrapment efficiency were calculated with the following equations [7]:

$$\textit{Entrapment efficiency} = \frac{(\textit{Total mount of drug} - \textit{amount of unbound drug}) \; X \; 100}{\textit{Total amount of drug}}$$

DRUG LOADING OF NANOPARTICLES

The drugs´ loading capacity was calculated by comparison of practically loaded drug found in the analysis of nanoparticle solution with that of the theoretical amount of drug taken in beginning to load in the polymer shown in the following equation. 20 mg of dried nanoparticles was accurately transferred and dissolved in acetone, which was then diluted appropriately and analyzed by the developed HPLC method and calculated from the following equation:

$$\textit{\% Drug loading} = \frac{\textit{Amount of drug found X } 100}{\textit{Amount of drug and polymer}}$$

PARTICLE SIZE AND SURFACE CHARGE ANALYSIS

The electrokinetic stability and size uniformity of the nanoparticles were investigated, zeta potential and particle size for the formulations of gliclazide and linagliptin were measured by photon correlation spectroscopy employing a Zetasizer (Malvern Instruments, Malvern, UK). Each sample was measured in triplicate. All analyses were performed on samples adequately diluted with filtered deionized water. All determinations were performed in triplicate. Results are reported as mean ± SD

TRANSMISSION ELECTRON MICROSCOPE STUDY

Transmission electron microscopy (TEM) was done with a JEM-2100 electron microscope (JEOL, Tokyo, Japan).

IN VITRO DRUG RELEASE STUDIES

A weight of prepared nanoparticles equivalent to 5mg of linagliptin and 60 mg of gliclazide was subjected to release study, using a dialysis membrane [8] (mass cut-off of 12 KDa). The bags were secured and introduced in the baskets of USP dissolution tester apparatus type I, rotated at 100 rpm in 250ml of phosphate buffer medium with pH 7.4. The percent released at the interval time of 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 20, and 24 h was determined. Aliquots of 1 ml were taken and replaced with fresh medium to maintain sink condition then the subjects were analyzed using the developed HPLC method. The released amount of each drug was measured and calculated.

STATISTICAL ANALYSIS

Results are being represented as mean ± standard deviation (SD). GraphPad InStat® program was used for determination of residual standard deviation of linearity and determination of limit of detection LOD and limit of quantitation LOQ

RESULTS

HPLC FOR SEPARATION OF LINAGLIPTIN AND GLICLAZIDE AND VALIDATION

The method was successively employed and system suitability parameters for the chromatographic separation of linagliptin and gliclazide were determined before analysis of the actual samples. Parameters included tailing factor

Table I. Gradient flow of mobile phases A and B

Time (min)	Mobile phase A concentration	Mobile phase B concentration
0.1	65	35
2.7	65	35
2.71	45	55
3.7	45	55
3.71	25	75
5.7	25	75
5.71	65	35
8.0	65	35

Table II. Formulae of nanoparticles

Formula	Polymer: drugs	HPMC weight (mg)	Xanthan gum weight (mg)
GLH1	0.5: 1	325	--
GLH2	1: 1	650	--
GLH3	2: 1	1300	--
GLX1	0.5: 1	--	325
GLX2	1: 1	--	650
GLX3	2: 1	--	1300
GLHX1	0.5: 1	162.5	162.5
GLHX2	1: 1	325	325
GLHX3	2: 1	650	650

Table III. Represents the system suitability of the developed HPLC method; (n=5)

Item name	Criteria	Linagliptin	Gliclazide
Number of theoretical plates	Not less than 2000	3622±3.26	24288±2.67
Tailing factor	Not more than 2	0.93±0.01	1.17±0.03
Capacity factor	Not less than 2	2.54±0.02	4.79±0.02
Resolution	Not less than 2	4.26±0.01	23.81±0.11

Table IV. Validation parameters of analytical method

Parameter		Linagliptin results	Gliclazide results
Linearity	Correlation coefficient R^2	0.9992	0.9993
	Slope	1546.54	3349.7
	Intercept	- 3012.32	-9886.6
Accuracy	Mean % recovery± SD	99.81 % ± 0.27	99.26 % ± 0.41
	Range	4:160 µg/ml	24:960 µg/ml
Precision	Intraday (RSD %)	0.39	0.57
	Interday (RSD %)	0.62	0.93
Sensitivity	Limit of detection	5.91 µg /ml	37.26 µg /ml
	Limit of quantitation	17.91 µg /ml	112.89µg /ml
Specificity	Recovery % in 0.1 N HCl	92.11 % ± 0.68	86.31 % ± 0.68
	Recovery % in 0.1 N NaOH	93.52 %± 0.54	95.67 %± 0.54
	Recovery % in 10% H_2O_2	90.16 % ± 0.96	89.96 % ± 0.96
Robustness	pH 2.5 (RSD%)	0.32	0.48
	pH 3.5 (RSD%)	0.37	0.69
	Flow rate 1.4 mL/min (RSD %)	0.41	0.58
	Flow rate 0.6 mL/min (RSD %)	0.66	0.83
	Column temperature 45 (RSD %)	0.39	0.42

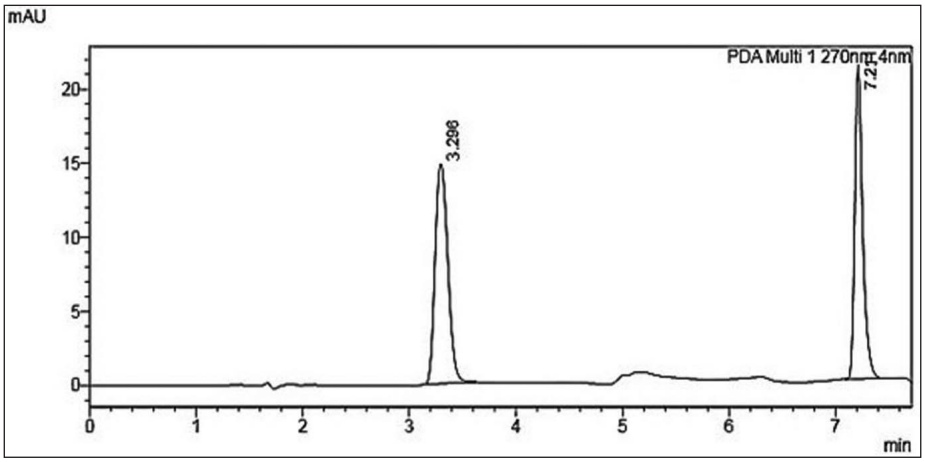

Fig 1. HPLC spectrum of gliclazide and linagliptin

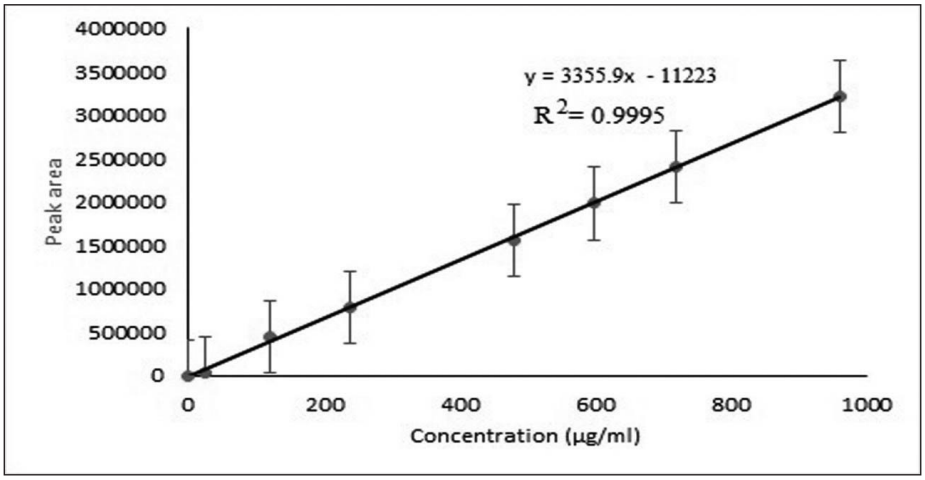

Fig. 2. Calibration curve of gliclazide

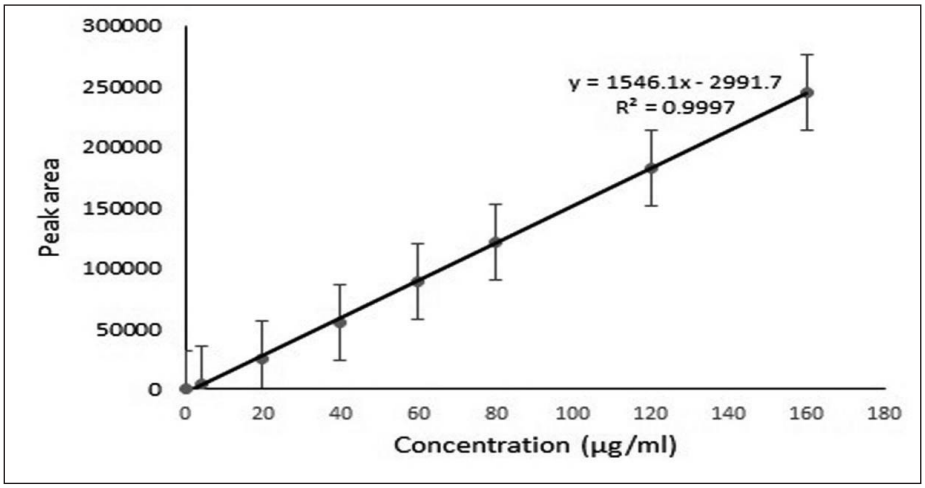

Fig. 3. Calibration curve of linagliptin

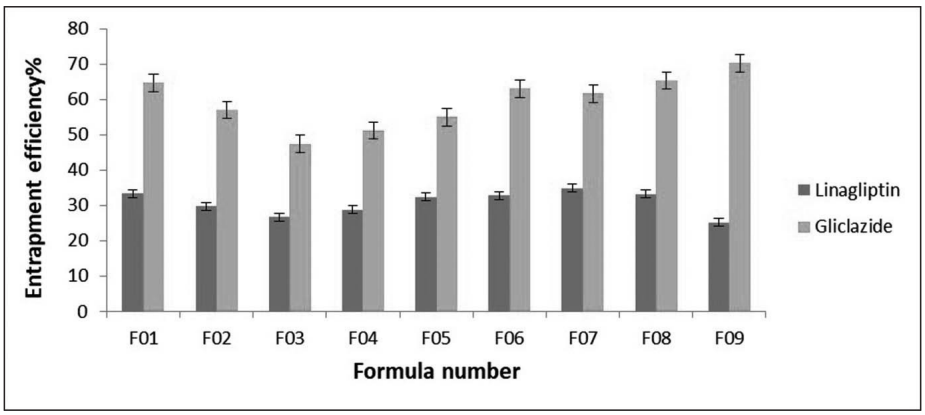

Fig 4. Entrapment efficiency of gliclazide compared with linagliptin

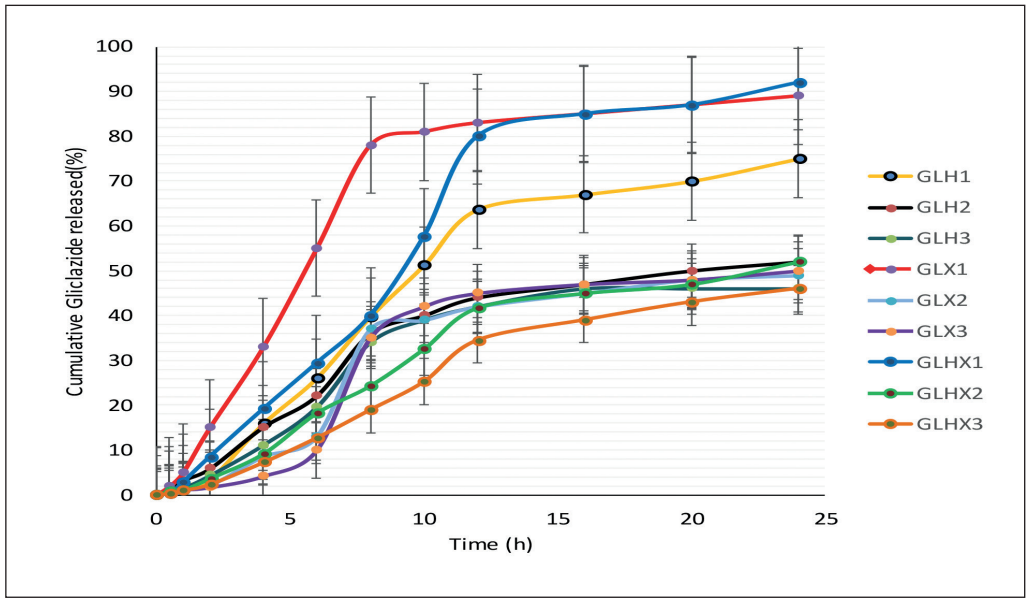

Fig 5. Dissolution rate of linagliptin from the prepared nanoparticles (values represent mean ±SD, n=6)

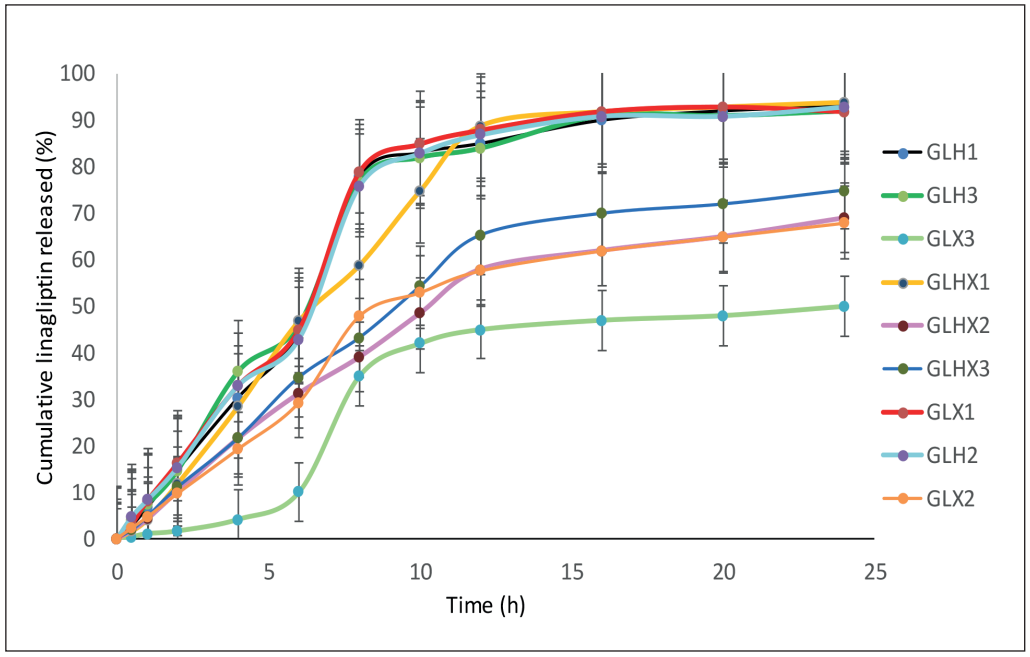

Fig. 6. Dissolution rate of gliclazide from the prepared nanoparticles (values represent mean ±SD, n=6)

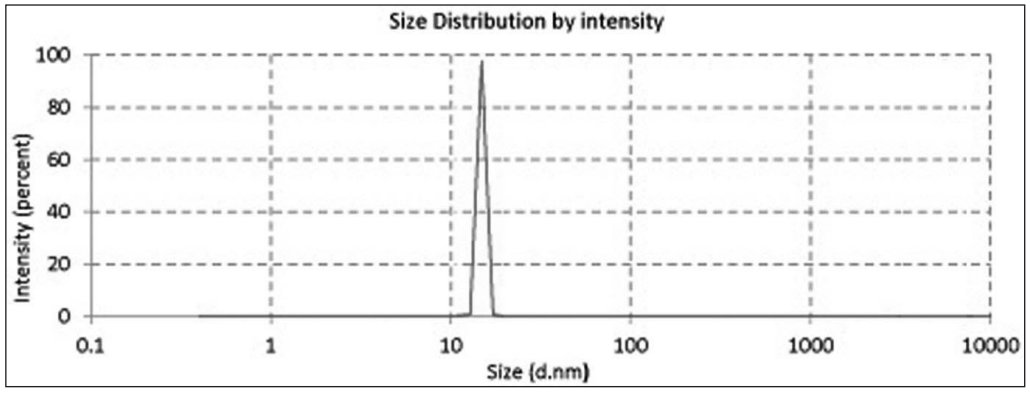

Fig. 7. Size distribution of the selected formula GLX1.

(T) should not be more than 2, resolution (R_S) should be more than 2, capacity factor (k') should be more than 2 and plate count should be not less than 2000 [9]. The resulted parameters were within limits shown in Fig.1 and Table III.

Recovery and accuracy were determined by preparing serial dilution of both linagliptin and gliclazide standard solution. 10.7mg of linagliptin and 60mg of gliclazide were dissolved in a mixture of phosphate buffer pH 6.8 in ratio with acetonitrile of 65: 35. The serial dilutions were

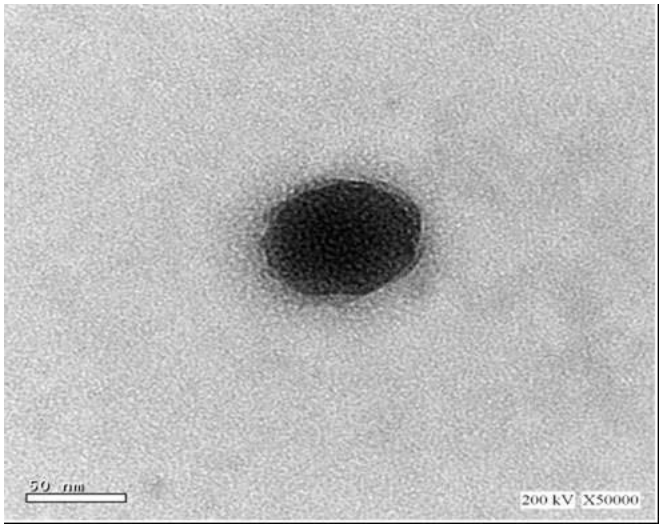

Fig. 8. TEM Photograph of the selected formula nanoparticles in 50 nm scale

prepared to be (4, 20, 40, 60, 80, 120, 160 μg/ml) and (24, 120, 240, 480, 600, 720 and 940 μg/ml) to represent the following ratios (5, 25, 50, 75, 100, 150 and 200%). All the validation parameters were done according to the international conference. Harmonization ICH [10] and USP [11] were shown in Table IV and Fig 2 and 3.

The correlation coefficient (r2) was found to be >0.999 which was within the limits specified (not less than 0.99). The recovery was found to be in the range of 98–102%, that indicates this method can be used for quantitative routine quality control analysis of pharmaceutical dosage forms. The precision of a method determines the closeness of agreement between a series of measurements of the same sample. The RSD values were found to be less than 1% within the generally accepted limit of <2%. Hence, confirming the good precision of the assay method. The sensitivity of the method was measured by calculating the limit of detection (LOD) and limit of quantification (LOQ) [12] for gliclazide and linagliptin using GraphPad InStat® to be 37.26 μg/ml, 112.89 μg /ml, 5.91 μg/ml, and 17.91 μg/ml, respectively. The results were shown in Table IV and Fig. 2 and 3.

CHARACTERIZATION OF NANOPARTICLES PREPARED

DETERMINATION OF ENTRAPMENT EFFICIENCY

The drug content of gliclazide was ranged from 11.5% to 24.9% while linagliptin was ranged from 0.49% to 1.07%. The entrapment efficiency of gliclazide was from 70.19% to 47.44% while linagliptin ranged from 25.19 to 34.80 as shown in Table V, Fig. 4. Efficiency entrapment of gliclazide was about two times of linagliptin, which may be since gliclazide was added about 12 times of linagliptin. The amount of gliclazide was found in all formulae 24 times the amount of linagliptin which reached the ratio of linagliptin to gliclazide 2.5mg/60mg except in formula GHX3. Hence, these results emphasize that the desired strength was achieved in the majority of formulae.

The polydispersity index (PDI) was not uniform in GLH1-GLH3 ranging from 0.54 to 0.97. However, in the case GLX1-GLX3, PI values ranged from 0.48 to 0.56 indicating uniformity of the particle size distributions.

IN VITRO RELEASE STUDY OF PREPARED NANOPARTICLES

The release of linagliptin from GLH1, GLX1, and GHX1 was more than 75% after 8 h, then showing plateau while one formula only showed release of gliclazide more than 80% after 8 h. So, the best formula was GHX1, which showed acceptable release of more than 80% of gliclazide and linagliptin after 8 h and prolonged for 24 h.

KINETIC OF THE IN-VITRO RELEASE DATA

To describe the release that best correlation coefficient fitting the profile of drugs release from its di-loaded nanoparticles, the in-vitro release data were fitted to zero order, first order, and diffusion-controlled release mechanisms according to Higuchi model [13] as follows:

(a) Zero-order kinetic model:
$C = C_o - K_o t$

(b) First-order kinetic model:
$\log C = \log C_o - K t/2.303$

(c) Higuchi diffusion model:
$Q = kt^{½}$

where

C_o = initial drug concentration, C = remaining drug concentration at time t.

t = time of release

K_o = zero order rate constant, K = first order rate constant

Q = amount of drug released/unit area, Q = amount of drug released/unit are

The highest correlation coefficient is used to select of the mechanism of release. Further evidence proof of diffusion was performed by analyzing the data using the following equation [14]:

$Mt/M\infty = K . t^{n}$

Where $Mt/M\infty$ is the fraction of drug released at time t, K is a constant including structural and geometric characteristics and n – the release exponent characteristic for the drug transport mechanism. When n = 0.5 Fickian diffusion is observed and the release rate-independent on t, while 0.5 < n < 1.0 indicate anomalous (non-Fickian) transport and when n = 1, the release is zero-order [14,15]. Korsmeyer-Peppas plots that showed acceptable linearity (R2 values between 0.95 and 0.98), with slope values less than 0.5, indicating that the drug release mechanism from the selected tablets was diffusion controlled shown in Table VI.

The TEM image of the obtained nanoparticles of formula GLHX1 is shown in Fig. 8. No obvious agglomerate of the nanoparticles can be found. The scale of field nanoparticle is in the range of 50 nm which emphasized good sizes and morphology. The nanoparticles showed a smooth surface and spherical shape. Fig. 8 showed the TEM photograph of nanoparticles.

Table V. Mean particle size, production yield, drug content, ratio of linagliptin to gliclazide, zeta potential and Polydispersity index (PDI) of nanoparticles

Formula	Drug Content* (%) ± SD		Ratio of linagliptin to gliclazide	Production Yield* (%) ± SD	Zeta Potential* (mV) ± SD	Mean particle size* (nm) ± SD	Polydispersity index PDI*
	Gliclazide	linagliptin					
GLH1	24.9±0.1	1.07±0.03	0.0429	82.50±0.21	-12.2±0.05	523±0.09	0.63±0.01
GLH2	18.3±0.2	0.80±0.01	0.0434	83.02±0.35	-13.9±0.09	673±0.02	0.54±0.02
GLH3	11.5±0.1	0.54±0.04	0.0469	84.02±0.26	-14.6±0.08	813±0.01	0.97±0.02
GLX1	18.74±0.1	0.88±0.01	0.0469	83.00±0.32	-20.6±0.08	596±0.04	0.49±0.02
GLX2	17.28±0.05	0.85±0.02	0.0491	83.00±0.16	-21.1±0.10	428±0.05	0.48±0.01
GLX3	14.57±0.07	0.63±0.01	0.0433	88.02±0.24	-22.3±0.13	341±0.04	0.56±0.02
GLHX1	22.03±0.13	1.04±0.01	0.0472	85.00±0.37	-18.5±0.14	448±0.03	0.59±0.01
GLHX2	20.52±0.09	0.87±0.01	0.0424	83.02±0.29	-14.2±0.09	389±0.04	0.37±0.02
GLHX3	16.41±0.15	0.49±0.02	0.0299	86.99±0.38	-16.7±0.15	341±0.01	0.41±0.05

*All values are reported as mean ± standard deviation (SD), n=3.

Table VI. Kinetic modeling of gliclazide and linagliptin release from different nanoparticles formulae

Formula	Zero order R^2		First order R^2		Higuchi diffusion R^2		Korsmeyer-Peppas R^2		n*	
	G	L	G	L	G	L	G	L	G	L
GLH1	0.917	0.957	0.679	0.608	0.954	0.981	0.984	0.971	0.325	0.423
GLH2	0.969	0.955	0.753	0.752	0.945	0.951	0.954	0.953	0.112	0.149
GLH3	0.624	0.726	0.612	0.695	0.952	0.961	0.967	0.971	0.468	0.489
GHX1	0.899	0.912	0.798	0.815	0.956	964	0.962	0.970	0.463	0.476
GLX2	0.912	0.926	0.897	0.876	0.966	0.973	0.960	0.965	0.367	0.354
GLX3	0.829	0.885	0.764	0.789	0.953	0.965	0.982	0.991	0.462	0.463
GLHX1	0.906	0.911	0.847	0.862	0.967	0.974	0.980	0.983	0.327	0.361
GLHX2	0.865	0.895	0.793	0.799	0.974	0.975	0.992	0.994	0.432	0.443
GLHX3	0.869	0.933	0.838	0.815	0.962	969	0.971	0.970	0.325	0.337

R^2 = correlation coefficient, and n is the release exponent obtained from Korsmeyer-Peppas equation.

Also, the nanoparticles have core and shell structures.

The literature lacks trials to assay gliclazide and linagliptin in combination, perhaps due to the absence of gliclazide and linagliptin combination in the market. In this work we tried to assay both gliclazide and linagliptin in the same time without any interference using reversed-phase HPLC. Also, we succeeded to prepare di-loaded gliclazide and linagliptin nanoparticles formulations which is the first trial to formulate both in combination. However, some researches were conducted to formulate gliclazide alone in nanoparticles. Dhome et al, [16] prepared gliclazide solid lipid nanoparticles using Phospholipon 90. The optimized formula released about 61% of particles after 8 h.

Also, some papers were published to try to formulate linagliptin sustained release nanoparticles. Navaneetha K. et al [17], formulated and in-vitro evaluated nanoparticles of linagliptin. Nanoparticles containing polycaprolactone and polyvinyl alcohol (PVA) nanoparticles were prepared by solvent evaporation method showing efficient entrapment and the formulae showing good sustained release.

DISCUSSION

A HPLC method was developed and validated successfully to analyze both gliclazide and linagliptin in combination regarding analytical validation parameters in accordance with ICH and USP.

The zeta potential of the nanoparticles containing HPMC polymer GLH1-GLH3 was in range -12.2 to -14.6 mV and GLHX1-GLHX3 the range was from – 14.2 to -18.6 mV while GLX1 – GLX3 (the formulae containing xanthan alone in different percentage) had the best zeta potential which ranged 20.6-22.3 mV which are close to ideal stabilization of -25 mV due to the negative charge on terminal carboxyl group on xanthan [18, 19]. Fortunately, the best formula GHX1 which showed the appropriate release profile had a zeta potential of -20.6 mV, which indicates stability and dividing of aggregation between other nanoparticles on time. The spherical shape of di-loaded nanoparticles with no aggregation was confirmed by a TEM study showing smooth surfaces. The release of linagliptin from GLH1, GLX1 and GHX1 was more than 75% after 8 h and prolonged to 24h, while one formula only showed

release of both gliclazide and linagliptin more than 80% after 8 h. So, the best formula was GHX1 which showed acceptable release of more than 80% of gliclazide and linagliptin after 8 h and prolonged for 24 h.

CONCLUSIONS

The formula GHX1 containing 0.5:1 xanthan gum makes drugs, that have the best nanoparticles formula which released more than 75% of both drugs after 8 h. Xanthan gum could help to formulate stable nanoparticles with high zeta potential, good morphology and prolong the releasing of both drugs for 24 h. So, the formula could be suitable for extended-release of gliclazide and linagliptin over 24 h for once daily administration.

REFERENCES

1. Mahendra L., Birendra S.J. Formulation and in vitro evaluation of modified release gliclazide tablet. Chem Pharm Res. 2011;3:348-352.
2. Rubina R.C., Pius C.R., Manju S., Shobana M. Formulation and Characterization of Gliclazide Nanosuspension. Research J Pharm and Tech. 2021;14: 779-786.
3. More C.G., Dabhade P.S., Jain N.P., Aher P.O. Solubility and dissolution enhancement of gliclazide by solid dispersion technique, Int J Pharm Chem Anal. 2015;2: 51-58.
4. Han E., Lee M., Lee Y. et al. Effect of Switching from Linagliptin to Teneligliptin Dipeptidyl Peptidase-4 Inhibitors in Older Patients with Type 2 Diabetes Mellitus. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy. 2020;13: 4113–4121.
5. Jentadueto (linagliptin and metformin). Summary of product characteristics, 2014. https://www.rxlist.com/jentadueto-drug.htm [data access 18.05.2021].
6. Thomas L., Eckhardt M., Langkopf E. et al. (R)-8-(3-amino-piperidin-1-yl)-7-but-2-ynyl-3-methyl-1-(4-methyl-quinazolin-2-ylmethyl)-3,7-dihydro-purine-2,6-dione (BI 1356), a novel xanthine-based dipeptidyl peptidase 4 inhibitor, has a superior potency and longer duration of action compared with other dipeptidyl peptidase-4 inhibitors. J Pharmacol Exp Ther. 2008; 325: 175- 82.
7. Ibrahim M., Shazly G., Aleanizy F. et al. Formulation and evaluation of docetaxel nanosuspensions: In-vitro evaluation and cytotoxicity, Saudi Pharm J. 2019;27: 49-55.
8. Jourghanian P., Ghaffari S., Ardjmand M. et al. Sustained release curcumin loaded solid lipid nanoparticles, Adv. Pharm. Bull. 2016;6: 17-21.
9. Epshtein N.A. Validation of Chromatographic Methods: Determining the Limit of Quantification in Practice, Pharm Chem J. 2021;55: 91–96.
10. ICHHT guideline. International Conference on Harmonization ICH Q 2A. Text on validation of analytical procedures: methodology. 2005, 400p.
11. The Pharmacopoeia of United States of America. 42th Ed. Mack publishing Co. Easton. 2019; 2.
12. Bayoumi A. Enhancement of solubility of a poorly soluble antiplatelet aggregation drug by cogrinding technique, Asian J Pharm Clin Res. 2018;11: 340-344.
13. Higuchi B. Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices; J. Pharm. Sci. 1963;52: 1145-1149.
14. Korsmeyer R.W., Gurny R., Docler E. et al. Mechanism of solute release from porous hydrophilic polymers. Int. J. Pharm. 1983; 15: 25-35.
15. Korsmeyer R.W., Peppas N.A. Macromolecular and modeling aspects of swelling-controlled systems. Controlled Release Delivery Systems, Dekker, New York, N.Y. 1983, 101 p.
16. Dhome A., Deshkar S., Shirolkar S. Gliclazide solid lipid nanoparticles: Formulation, Pharmaceutical Resonance. 2018;1:8-16.
17. Navaneetha K., Navya A., Reddy V.B. et el. Formulation and in-vitro evaluation of nanoparticles of linagliptin. World J Pharm Res. 2017;6: 1319-1328.
18. Shah P., Chavda K., Vyas B., Patel S. Formulation development of linagliptin solid lipid nanoparticles for oral bioavailability enhancement: role of P-gp inhibition. Drug Deliv Transl Res. 2021;11: 1166-1185.
19. Sahu P.B., Das K.M. Nanosuspension for enhancement of oral bioavailability of felodipine. Appl Nanosci. 2014; 4: 189–197.

Contributionship:
Firas Aziz Rahi [A,D,F]
Muath Sheet Mohammed Ameen [B,D,E]
Mohammed Shamil Fayyad [C,D,F]

Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR

Firas Aziz Rahi
Al-Turath University College
Mansour, 27134 Baghdad, Iraq
e-mail: firas.aziz@turath.edu.iq

Received: 29.06.2021
Accepted: 31.08.2021

A – Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article