RESEARCH ARTICLE

Formulation, Evaluation, Compatibility and *In-vitro* Study of Bilayer Tablet by Model Fitting

Sudarshan B. Kakad*, Punit R. Rachh

Bhagwant University, Ajmer, Rajasthan, India.

Received: 19th June, 2022; Revised: 20th July, 2022; Accepted: 21st August, 2022; Available Online: 25th September, 2022

ABSTRACT

Objective: To develop a bilayer tablet containing sustained release metformin HCl and immediate release vildagliptin and to study the compatibility study as well as release kinetics of formulation by model fitting.

Methods: The bilayer tablet comprises of two parts, immediate release Vildagliptin drug and sustained release Metformin HCl. Sustained release granules are prepared by using non-aqueous wet granulation techniques and immediate release granules are prepared by aqueous wet granulation and then both the granules are compressed at appropriate force to form a bilayer tablet. The drug release of prepared bilayer tablet is studied by *in-vitro* dissolution study and model fitting.

Results: Drug identification and compatibility study was performed by Fourier transform infrared spectroscopy (FT-IR). Post compression parameters of bilayer tablet showing appropriate results. *In-vitro* dissolution study shows more than 90% vildagliptin drug releases in 1-hour while maximum metformin drug releases after 10 hours. After applying model fitting, metformin gives r-value 0.9942 and vildagliptin gives r-value 0.9610 in matrix model.

Conclusion: Excipients used in the preparation of bilayer tablets was compatible with metformin HCl and vildagliptin. After studying *in-vitro* drug release by model fitting, both drugs pass through zero order, first order, Matrix, Peppas and Hixson-Crowell models but matrix model is the best model and vildagliptin shows immediate release effect and metformin HCl shows sustained release effect. The prepared bilayer tablet is used for the treatment of type-II diabetes mellitus.

Keywords: Bilayer, compatibility, Immediate release, Sustained release.

International Journal of Drug Delivery Technology (2022); DOI: 10.25258/ijddt.12.3.75

How to cite this article: Kakad, SB, Rachh, PR. Formulation, Evaluation, Compatibility and *In-vitro* Study of Bilayer Tablet by Model Fitting. International Journal of Drug Delivery Technology. 2022;12(3):1385-1389.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Solid oral dosage forms are the most advantageous and widely used route to deliver drugs due to ease of administration and flexibility of the design. Tablets are one of the most popular and acceptable dosage forms. Furthermore, controlled-release oral dosage forms are increasingly popular. Bilayer tablet is one of the type of tablet and it is suitable for sequential release of two drugs in combination, separate two incompatible substances and for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose. There is various application of the bi-layer tablet it consists of monolithic partially coated or multilayered matrices. In the case of bi-layered tablets, drug release can be rendered almost unidirectional if the drug can be incorporated in the upper non-adhesive layer its delivery occurs into the whole oral cavity.[1-3]

Diabetes is a chronic disease that occurs when the pancreas does not produce enough insulin or the body cannot effectively use the insulin it produces. Diabetes is one of the most common non-communicable diseases globally and has two types: Type-I and Type-II. Effective clinical maintenance of the type-II diabetic condition needs chronic treatment with oral hypoglycemic agents. Better control over the condition, need better systemic availability of drug, maintenance of plasma concentration of drug and, adherence of patient to standard treatment with better compliance.[4,5]

For effective clinical management of diabetes, it is important to maintain post-prandial blood sugar levels. In this study we are prepared a bilayer tablet containing two anti-diabetic drugs. Vildagliptin in the immediate release will help to reduce post-prandial blood sugar level and second one is metformin HCl, the only available biguanide, remains the first-line drug therapy for patients with type-II diabetes mellitus (T2DM), acting by decreasing the hepatic glucose output and peripheral insulin resistance.[5,6]

Author for Correspondence: sudarshankakad1990@gmail.com

MATERIALS AND METHODS

Vildagliptin and metformin HCl were received as gift samples while all other chemicals of analytical grade were procured from the market.

Preformulation Studies

Drug- Excipient Compatibility Study

Drug-excipient compatibility was performed to assess the suitability of excipients being used in the formulation using FT-IR spectroscopy.

Preparation of Bilayer Tablet

Preparation of IR Layer Granules for Compression[5]

Weighed quantity of drug pharmatose 200, pregelatinized starch, and croscarmellose sodium (half quantity) were passed through a sieve and mixed in a cage blender for 10 min. Accurately weighed PVP K-30 and sodium lauryl sulfate was dissolved in purified water to prepare a binder solution. Granules were prepared from the blend, dried and size reduced. Weigh remaining half quantity of croscarmellose sodium; avicel and aerosil were passed through a sieve. Iron oxide red was weighed, passed through a sieve, and mixed with extra granular material. Finally, prepared granules were lubricated by sodium stearyl fumarate.

Preparation of SR Granules for Compression[8,9]

Weigh accurately metformin HCl, HPMCK100M and avicel as per composition and passed through sieve and mixed homogeneously. Prepare the wet mass of this mixture by blending the solution. The wet mass passed through a sieve to get a uniform size granule and dried at 60°C. The obtained granules were mixed with magnesium stearate, and aerosil.

Bilayer Tablet Compression

The bilayer tablets were prepared by using tablet compression machine. The sustained release granules of metformin HCl were fed into the machine's die cavity and compressed into intermediate tablets under low pressure. Then immediate release granules of vildagliptin were fed into intermediate tablets and compressed to obtain a bilayer tablet.

Evaluation of Post Compression Parameters[5,10,11]

Weight Variation

Twenty tablets were weighed individually and average weight was determined. The individual tablet weight was compared with average tablet weight. For sustained release, tablet weight is 900.00 mg and the maximum percent difference allowed is 5.0% *i.e.,* ± 45.00 mg.

Friability Test

Friability for the sustained release tablets was determined by 100 revolutions at 25 rpm. The friability of the tablets should be less than 1%.

Hardness

Tablet was selected randomly from individual formulations and hardness was measured using a digital hardness tester.

Table 1: Composition of optimized bilayer tablet containing IR vildagliptin layer and SR Metformin HCl

Ingredient	*Quantity/Tablet (mg)*
Vildagliptin	50.00
Pharmatose 200	136.50
Pregelatinised starch	24.00
Povidone	5.00
Sodium Lauryl Sulphate	1.00
Cross carmellose sodium	15.00
Avicel (pH 102)	15.00
Iron oxide red	1.00
Aerosil	1.00
Sodium Stearyl fumarate	1.50
Metformin HCl	500.00
HPMC K100 M	240.00
Lactose monohydrate	35.00
PVP K30	45.00
Magnesium Stearate	10.00
Aerosil	5.00
Avicel	15.00

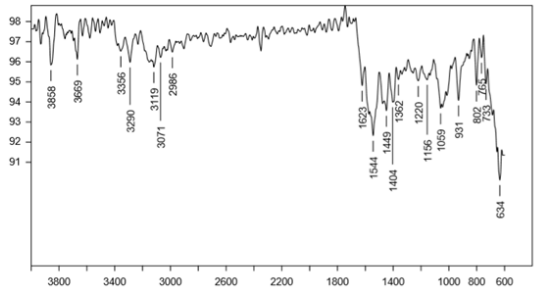

Figure 1: FTIR of Pure Metformin HCl

Dissolution Test

The tablets were evaluated for *in-vitro* drug release was carried out using USP dissolution apparatus.
The following conditions were applied.
USP Dissolution apparatus: Type II (Paddle)
Media: 0.1N HCl and pH 6.8 buffer
Volume of dissolution medium: 900 mL
Speed of paddle rotation: 75 RPM
Temperature : 37 ± 0.5°C
Sampling point : 5, 10, 15, 30, 45 min, 1, 2, 4, 6, 8, 10 and 12 hours

RESULT AND DISCUSSION

Drug Identification and Characterization

Fourier Transform Infra-Red (FT-IR) Analysis

A FT-IR spectrum of pure drug as shown in Figure 1. FT-IR of Metformin HCl showed characteristic sharp peaks at 3119, 3290, 3356 cm^{-1} due to N-H stretching vibrations, 1059 and 1156 cm^{-1} corresponding to C-N stretching, 634 cm^{-1} due to N-H wagging. The peaks observed in the FT-IR spectra of

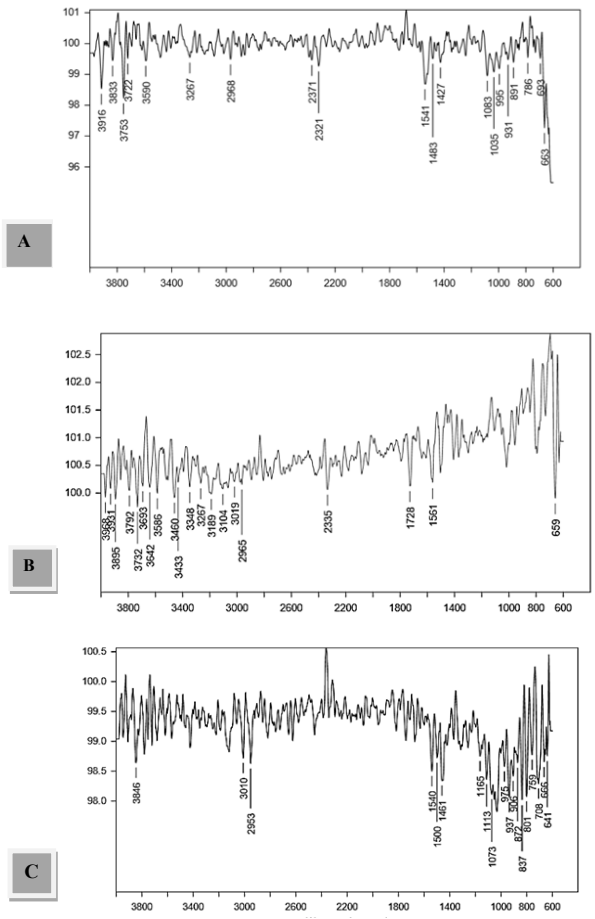

Figure 2: FT-IR spectra of (A) Metformin + HPMC K4M; (B) Metformin + HPMC K15M; (C) Metformin + HPMC K100M

pure drug were found to be matching with reported values for Metformin HCl, thus confirming the identity and purity of drug.

Drug-excipient Compatibility Study

The FT-IR spectra of drugs with excipients showed no change in the FT-IR pattern of all the functional groups of Metformin HCl. The peaks observed in the FT-IR spectra of pure drugs were found in FT-IR spectra of a physical mixture of drug and excipients. The spectra are given in Figure 2.

Evaluation of Bilayer Tablet

The prepared bilayer tablet is evaluated by using post compression parameters such as, average weight, hardness, percent drug and friability. The result is enlisted in Table 2 and Figure 3).

In-vitro Drug Release

The %cumulative drug release was evaluated for trial batches prepared by using selected batches of immediate release and

Table 2: Evaluation of post-compression parameter

Batch No.	*Avg. Tab Wt. (mg)*	*Hardness (Kg/cm²)*	*Assay (%)*	*Friability (%)*
Bilayer	1101 ± 0.74	7.8	100.2	0.42

Table 3: Dissolution profiles

Time (min)	*% Cumulative drug release*	
	IR vildagliptin	*SR Metformin HCl*
0	0	0
5	19.40	1.46
10	45.92	2.34
15	67.76	3.68
30	83.64	7.49
45	92.88	13.24
60	98.60	28.56
120		45.52
240		66.86
360		81.30
480		90.46
600		98.82

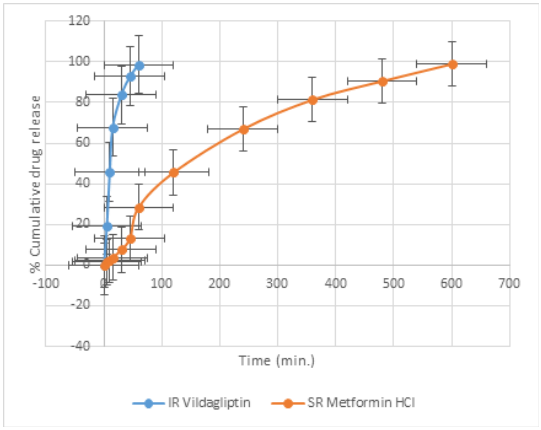

Figure 3: *In-vitro* drug release of bilayer tablet

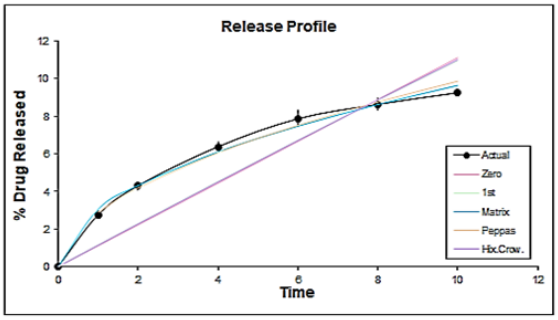

Figure 4: Percentage release of metformin HCl with model fitting

sustained release. The maximum amount of vildagliptin is release in initial one hour and initial time metformin drug release is slow (Table 3).

Percentage Release with Model Fitting

The release mechanism of metformin HCl and vildagliptin in formulations was studied by model fitting study. The data was obtained from *in-vitro* release studies into zero-order, first-order, Matrix, Peppas and Hixson-Crowell models (Figure 4 and 5).

After application, it was found that the optimized formulation S9 passes through zero order, first order, Matrix,

Table 4: Model fitting for Metformin: Residual sum of square

S. No.	*Time*	*Avg. % release*	*SD*	*Zero order*	*First order*	*Matrix*	*Peppas*	*Hixon-crowell*
1	0	0.000	0.00	0.000	0.000	0.000	-	0.000
2	1	2.752	0.17	2.693	2.557	0.087	0.020	2.603
3	2	4.302	0.17	4.330	4.041	0.000	0.014	4.137
4	4	6.370	0.21	3.716	3.381	0.076	0.102	3.491
5	6	7.856	0.38	1.421	1.292	0.154	0.120	1.334
6	8	8.626	0.28	0.067	0.053	0.000	0.016	0.057
7	10	9.246	0.04	3.460	2.890	0.152	0.375	3.068

Table 5: Model fitting for Vildagliptin: Residual sum of square

S. No.	*Time*	*Avg. % release*	*SD*	*Zero order*	*First order*	*Matrix*	*Peppas*	*Hixon-crowell*
1	0	0.000	0.00	0.000	0.000	0.000	-	0.000
2	5	8.872	3.80	19.325	6.294	53.378	27.869	10.489
3	10	23.255	7.02	204.579	119.546	0.141	1.317	148.940
4	15	35.081	7.85	468.848	295.164	49.839	40.716	354.329
5	30	44.684	7.82	317.840	146.102	25.563	0.023	196.967
6	45	51.616	6.67	128.424	48.358	9.499	43.430	69.320
7	60	57.985	3.60	18.264	11.679	3.775	145.466	13.630
8	90	60.667	1.62	396.020	75.865	63.526	916.032	124.855

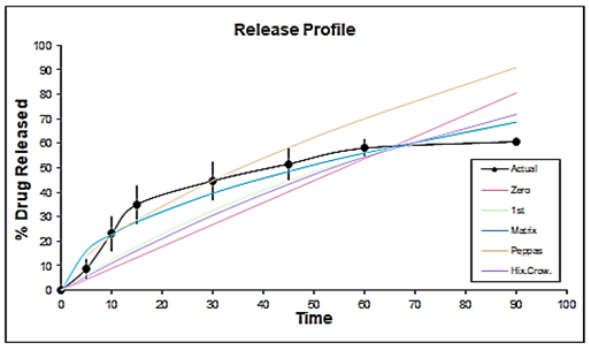

Figure 5: Percentage release of vildagliptin with model fitting

Peppas and Hixson-Crowell models based on figure and sustained drug release as indicated by the r-value 0.8791, 0.8896, 0.9961, 0.9942, 0.8861, respectively. The pharmacokinetic data for metformin was studied and on the basis of r-value, we conclude that Matrix model is the best model. Thus, the sustained release matrix tablet formulation displayed release of required quantity of drug with predetermined kinetics in order to maintain an effective drug plasma concentration. The pharmacokinetic data of the metformin release from the bilayer tablet are described in Table 4.

After application, it was found that the optimized formulation I10 passes through zero order, first order, Matrix, Peppas and Hixson-Crowell models based on figure and sustained drug release as indicated by the r-value 0.7303, 0.8583, 0.9610, 0.9319, 0.82.25, respectively. The pharmacokinetic data for vildagliptin was studied and on the basis of r-value, we conclude that Matrix model is the best model. Thus, the immediate release matrix tablet formulation displayed release of required quantity of drug after bursting the tablet due to superdisintegrant with predetermined kinetics in order to maintain an effective drug plasma concentration. The pharmacokinetic data of the vildagliptin release from the bilayer tablet are described in Table 5.

CONCLUSION

The present study involved formulation of bilayer tablet containing sustained release metformin HCl and immediate release vildagliptin and compatibility study as well as release kinetics of formulation by model fitting. Bilayer tablet is formulated by using sustained release granules are prepared using non-aqueous wet granulation techniques and immediate release granules are prepared by aqueous wet granulation. After FT-IR study and model fitting technique, we conclude that, excipients used in the preparation bilayer tablets were compatible with metformin HCl and vildagliptin. Both the drugs pass through zero order, first order, Matrix, Peppas and Hixson-Crowell models but the Matrix model is the best model and Vildagliptin shows immediate release effect and metformin HCl shows sustained release effect. Therefore, the prepared formulation will offer a better therapeutic regimen and gives good post-prandial hypoglycemic management.

REFERENCES

1. Vishal M, Anuj K, Pankaj P, Deepti P, Shraddha S, Mansee S, et al. Formulation development and evaluation of bilayer tablets of lornoxicam. Int J Drug Dev Res. 2012, 4(2),173–9.
2. Sudarshan B. Kakad, and Dr. Punit R. Rachh, A review on Bi-layer tablet: an emerging trend, European Journal of Pharmaceutical and Medical Research, 2019,6(8), 223-229.
3. Luo, D.; Kim, J. H.; Park, C.; Oh, E.; Park, J. B.; Cui, J. H.; Cao, Q. R.; Lee, B. J. Design of Fixed Dose Combination and Physicochemical Characterization of Enteric-Coated Bilayer

Tablet with Circadian Rhythmic Variations Containing Telmisartan and Pravastatin Sodium. Int. J. Pharm, 2017; 523(1): 343–356.

4. Chatterjee S, Jat RK, Formulation and Evaluation of Immediate Release Tablet Dosage Form of Linagliptin and Metformin Hydrochloride, Journal of Drug Delivery and Therapeutics. 2021; 11(3-S):61-64
5. Kakad SB, Rachh PR. Design, Development and Characterization of Immediate Release Matrix Tablet of Vildagliptin. International Journal of Pharmaceutical Quality Assurance. 2021;12(4):303-308.
6. Deepika Kathuria, Akshay D. Raul, Pravin Wanjari, Prasad V. Bharatam, Biguanides: Species with versatile therapeutic applications, European Journal of Medicinal Chemistry
7. Rablee S, Bhanu Pratap S, Development and Evaluation of Bilayer Tablets for Immediate and Controlled Release of Metformin Hydrochloride, Int J Curr Pharm Res, 2017;9 (5): 173-179.
8. Rajesh A and Yadav N, Pharmaceutical Processing – A Review on Wet Granulation Technology, International Journal of Pharmaceutical Frontier Research, April-June 2011; 1(1):65-83.
9. Kakad, S. B., & Rachh, P. R. Effect of hydrophilic polymer and binder on drug release of metformin HCl sustained release tablet. International Journal of Health Sciences, 2022; 6(S3), 6635–3343.
10. Pingale PL, Peddireddy N, Effect of Natural Polymer On Release Retarding rate of Glimepiride sustained release tablet, AdvSci Res, 2021; 12 (1) Suppl 1: 145-150.
11. Indian Pharmacopoeia, Government of India Ministry of Health and family welfare, 2018 edition, 308.