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FORMULATION DEVELOPMENT AND EVALUATION OF BILAYER TABLETS OF ANTIDIABETIC DRUGS

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ABSTRACT

The present study was aimed at the formulation development and evaluation of bilayer tablets containing antidiabetic drugs, metformin and saxagliptin, for the effective management of type 2 diabetes mellitus. The bilayer tablet was designed to provide an immediate release of metformin for rapid reduction of blood glucose levels and a floating sustained release of saxagliptin for prolonged therapeutic effect. The powder blends of both layers were evaluated for pre-compression parameters such as bulk density, tapped density, Carr's index, and Hausner's ratio to determine their flow properties. The prepared tablets were further evaluated for post-compression parameters including hardness, friability, thickness, weight variation, drug content, and in-vitro disintegration time. The metformin immediate release layer showed rapid disintegration with optimized formulation IF7 exhibiting a disintegration time of 40 ± 5 seconds. The saxagliptin floating sustained release tablets showed acceptable physical characteristics and demonstrated floating lag time ranging from 28 to 42 seconds with total floating duration greater than 12 hours. The optimized bilayer tablet showed satisfactory hardness (5.9 ± 0.3 kg/cm²), friability below 1%, and uniform drug content for both drugs. *In-vitro* dissolution studies revealed that the immediate release layer released 96.65% of metformin within 15 minutes, whereas the floating sustained release layer of saxagliptin showed a controlled drug release of 98.78% over 12 hours. The results indicate that the developed bilayer floating tablet system successfully achieved rapid onset of action along with sustained drug release. Therefore, the formulated bilayer tablets of metformin and saxagliptin may provide improved therapeutic efficacy, prolonged drug action, and better patient compliance in the treatment of type 2 diabetes mellitus.

Keywords: Bilayer tablet, Metformin, Saxagliptin, Floating drug delivery system, Sustained release, Immediate release, Type 2 diabetes mellitus, *In-vitro* dissolution.

INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from defects in insulin secretion, insulin action, or both. It is one of the most prevalent endocrine disorders worldwide and is associated with serious complications such as cardiovascular diseases, nephropathy, neuropathy, and retinopathy if not properly managed. The global prevalence of diabetes has increased rapidly in recent decades, making it a major public health

concern. Effective management of diabetes requires maintaining normal blood glucose levels through lifestyle modification and pharmacological therapy (World Health Organization, 2016).

Among oral antidiabetic drugs, Metformin is considered the first-line therapy for the treatment of type 2 diabetes mellitus. Metformin belongs to the biguanide class and primarily acts by reducing hepatic glucose production and improving insulin sensitivity in peripheral tissues. It also decreases intestinal glucose absorption, thereby contributing to improved glycemic control. Due to its efficacy, safety profile, and low risk of hypoglycemia, metformin is widely prescribed as an initial pharmacological treatment for patients with type 2 diabetes (American Diabetes Association, 2022).

Another important class of oral antidiabetic agents is the dipeptidyl peptidase-4 (DPP-4) inhibitors, among which Saxagliptin is commonly used. Saxagliptin acts by inhibiting the DPP-4 enzyme, which results in increased levels of incretin hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). These hormones enhance insulin secretion and suppress glucagon release in a glucose-dependent manner, thereby improving glycemic control. Combination therapy of metformin with saxagliptin has been shown to provide superior therapeutic outcomes compared with monotherapy due to their complementary mechanisms of action (Scheen *et al.,* 2010).

In recent years, bilayer tablet technology has emerged as an advanced drug delivery system for combination therapy. Bilayer tablets consist of two distinct layers, each containing different drugs or the same drug with different release profiles. This technology allows the formulation of an immediate-release layer to provide rapid therapeutic action and a sustained-release layer to maintain prolonged drug release. Such systems are particularly useful in chronic diseases like diabetes where maintaining consistent plasma drug levels is essential for effective management (Abdul *et al.,* 2004).

Bilayer tablets offer several advantages including separation of incompatible drugs, controlled drug release, improved therapeutic efficacy, and enhanced patient compliance. In the case of metformin and saxagliptin, bilayer tablets can provide rapid onset of action through the immediate release layer while maintaining prolonged glycemic control through sustained drug release. This approach reduces dosing frequency and improves patient adherence to long-term therapy (Shiyani *et al.,* 2008).

The formulation of bilayer tablets requires careful selection of excipients, polymers, and manufacturing techniques to ensure proper layer adhesion, mechanical strength, and desired drug release characteristics. Polymers such as hydroxypropyl methylcellulose (HPMC), ethyl cellulose, and carbopol are commonly used to control drug release. The developed tablets are evaluated for various quality control parameters such as hardness, friability, weight variation, drug content uniformity, disintegration time, and in-vitro drug release profile to ensure their stability and effectiveness (Aulton *et al.,* 2018).

Therefore, the formulation development and evaluation of bilayer tablets containing metformin and saxagliptin represents a promising strategy for improving therapeutic

efficacy and patient compliance in the management of type 2 diabetes mellitus.

MATERIALS AND METHODS

Materials

Metformin hydrochloride and saxagliptin were used as the active pharmaceutical ingredients for the preparation of bilayer tablets. Various excipients were used to achieve immediate and sustained drug release characteristics. Polymers such as hydroxypropyl methylcellulose (HPMC) were used for sustained release of saxagliptin, while sodium bicarbonate and citric acid were used as gas-generating agents to impart floating properties to the tablets. Microcrystalline cellulose (MCC) was used as a diluent, polyvinylpyrrolidone (PVP) as a binder, and magnesium stearate and talc were used as lubricant and glidant, respectively. All chemicals and reagents used in the study were of analytical grade and were obtained from reliable pharmaceutical suppliers.

Methods

Preparation of Instant Layer of Meformin (Phase-1)

Instant release tablets of Meformin were prepared by direct compression method after incorporating different superdisintegrants such as, crosscarmellose sodium (Ac-Di-Sol), crospovidone and sodium starch glycolate in different concentrations. The ingredients given below were weighed and mixed in geometric progression in a dry and clean mortar. Then the ingredients were passed through mesh #60 (Kumar *et al.,* 2007).

Method for Preparation of gastro retentive floating tablet of Saxagliptin

Direct compression was followed to manufacture the gas generating floating tablets of Saxagliptin. Nine different formulations (F1, F2, F3, F4, F5, F6, F7, F8, & F9) were prepared by direct compression. All the polymers selected, drug and excipients were passed through sieve no. 40 before using into formulation. The amount and ratio of drug and polymers were weighed as per given in table no. 2 and all the formulation were used for further evaluations parameters (Logidhasan *et al.,* 2013).

Evaluation of tablets

All the tablets were evaluated for following different parameters which includes;

General Appearance

Five tablets from different batches were randomly selected and organoleptic properties such as color, odor, taste, shape, were evaluated. Appearance was judged visually. Very good (+++), good (++), fair (+) poor (-), very poor (- -).

Thickness and diameter

Thickness and diameter of tablets were determined using Vernier caliper. Five tablets from each batch were used, and an average value was calculated.

Drug content

Twenty tablets were taken and amount of drug present in each tablet was determined. The tablets were crushed in a mortar and the powder equivalent to 100mg of drug was transferred to 100ml standard flask. The powder was dissolved in 50 ml of 0.1 N Hcl and made up to volume with of 0.1 N HCl. The sample was mixed thoroughly and filtered through a 0.45µ membrane filter. The filtered solution was diluted suitably and react with dye and analyzed for drug content by UV spectrophotometer at a λ_{max} of 214 nm using of 0.1 N HCl as blank (Munira *et al.,* 2015).

Hardness

For each formulation, the hardness of five tablets was determined using the Monsanto hardness tester (Cadmach).

Friability

The friability of a sample of 10 tablets was measured using a Friability tester (Electro Lab). Ten tablets were weighed, rotated at 25 rpm for 4 minutes. Tablets were reweighed after removal of fines (dedusted) and the percentage of weight loss was calculated (Gangwar *et al.,* 2015).

Uniformity of weight

Twenty tablets were randomly selected from each batch individually weighed, the average weight and standard deviation of 20 tablets was calculated.

***In vitro* buoyancy studies:**

In vitro buoyancy was determined by floating lag time as per the method described by Rosa *et al.* The tablets were placed separately in a 100 ml glass beaker containing simulated gastric fluid (SGF), pH 1.2 as per USP. The time required for the tablet to rise to the surface and float was determined as floating lag time.

Dissolution rate studies

In vitro drug release of the sample was carried out using USP- type II dissolution apparatus (Paddle type). The dissolution medium, 900 ml 0.1N HCl was placed into the dissolution flask maintaining the temperature of 37±0.5ºC and rpm of 75. One Saxagliptin tablet was placed in each basket of dissolution apparatus. The apparatus was allowed to run for 10 hours. Sample measuring 5 ml were withdrawn after every 1 hour up to 10 hours using 10ml pipette. The fresh dissolution medium (37ºC) was replaced every time with the same quantity of the sample. From this take 0.5 ml and dilute up to 10 ml with 0.1 N HCl take the absorbance at 214 nm using spectroscopy (Sachan *et al.,* 2016).

Formulation development of bilayer tablet

Optimized formulation IF-6 of Instant release layer (Meformin) and optimized formulation of F-5 (Saxagliptin) for control release used for formulation of Bi-layer tablet (Tiwari *et al.,* 2014).

Evaluation of bilayer tablets

All the tablets were evaluated for following different parameters which includes;

General Appearance

Five tablets from different batches were randomly selected and organoleptic properties suchas color, odor, taste, shape, were evaluated. Appearance was judged visually.

Very good (+++), good (++), fair (+) poor (-), very poor (- -).

Thickness and diameter

Thickness and diameter of tablets were determined using Vernier caliper. Five tablets from each batch were used, and an average value was calculated.

Hardness

For each formulation, the hardness of five tablets was determined using the Monsanto hardness tester (Cadmach).

Friability

The friability of a sample of 10 tablets was measured using a Friability tester (Electro Lab). Ten tablets were weighed, rotated at 25 rpm for 4 minutes. Tablets were reweighed after removal of fines (dedusted) and the percentage of weight loss was calculated.

Uniformity of weight

Twenty tablets were randomly selected from each batch individually weighed, the average weight and standard deviation of 20 tablets was calculated.

Drug content

Twenty tablets were taken and amount of drug present in each tablet was determined. The tablets were crushed in a mortar and the powder equivalent to 25 mg of Saxagliptin was transferred to 100ml standard flask. The powder was dissolved in 25 ml of 0.1 N HCl and made up to volume with 0.1 N HCl. The sample was mixed thoroughly and filtered through a 0.45µ membrane filter. The filtered solution was further diluted 0.1 ml to 10 ml suitably (10 ppm of Saxagliptin) and prepares individually 10 ppm solution of Meformin determine the Conc. of both drugs using 232nm and 214nm for Meformin and Saxagliptin respectively.

Dissolution rate studies

In vitro drug release was performed according to the USP dissolution apparatus II at 50 rpm and 37±0.5ºC temperature over a 12 hrs periods for Saxagliptin SR and 1 hr for Meformin IR, using an automated paddle dissolution system (Labindia). A minimum of 6 tablets per batch were tested.

The media used was 0.1N HCl at a pH 1.2 and a volume of 900 ml was maintained at 37±0.5˚C. Test sample (1ml) was withdrawn at particular time interval and replaced with fresh dissolution media maintained at the same temperature and the concentration of dissolved drug was determined using U.V. (Ultraviolet Labindia 3000+) spectrophotometer at λ_{max} 232nm for Meformin and 214 nm for Saxagliptin respectively.

RESULTS AND DISCUSSION

The powder blends prepared for the formulation of metformin immediate release tablets were evaluated for their pre-compression parameters to determine their flow properties before compression. The results are presented in Table 3. The loose bulk density of the formulations ranged from 0.335 to 0.352 g/ml, while the tapped bulk density ranged from 0.452 to 0.463 g/ml. The Carr's index values varied between 23.17% and 26.53%, and Hausner's ratio ranged from 1.302 to 1.361. These values indicate fair to good flow properties of the powder blends, which are suitable for direct compression of tablets.

The prepared metformin tablets were further evaluated for post-compression parameters such as hardness, friability, weight variation, thickness, and drug content, as shown in Table 4. The hardness of the tablets ranged from 3.1 to 3.3 kg/cm², indicating adequate mechanical strength. Friability values were below 1% for all formulations, demonstrating good resistance to abrasion during handling and transportation. All formulations passed the weight variation test, confirming uniformity in tablet weight. The thickness ranged from 3.3 to 3.7 mm, and the drug content was found between 96.65% and 99.45%, indicating uniform drug distribution in the tablets.

The in-vitro disintegration time of the metformin formulations was evaluated and the results are presented in Table 5. The disintegration time ranged from 40 to 97 seconds. Among all formulations, IF7 showed the fastest disintegration time (40 ± 5 seconds), which indicates a rapid release of the drug from the immediate release layer. This result suggests that IF7 may be considered as the optimized formulation for the instant release layer.

The floating sustained release layer of saxagliptin was also evaluated for pre-

compression parameters before tablet compression. The results shown in Table 6 indicate that the bulk density ranged from 0.415 to 0.441 g/ml and the tapped density ranged from 0.521 to 0.556 g/ml. The compressibility index values were between 19.54% and 22.57%, while Hausner's ratio ranged from 1.243 to 1.292. These results indicate acceptable flow properties of the powder blend, which are suitable for tablet formulation.

The post-compression parameters of saxagliptin floating sustained release tablets were evaluated and the results are summarized in Table 7. The hardness values ranged from 5.2 to 5.6 kg/cm², indicating adequate tablet strength. The friability values were below 1%, which confirms good mechanical stability. The drug content of all formulations ranged between 97.85% and 99.85%, which falls within acceptable pharmacopeial limits. All formulations exhibited a total floating duration of more than 12 hours, indicating the effectiveness of the floating system in maintaining buoyancy.

The buoyancy behavior of the saxagliptin floating tablets was further evaluated through in-vitro buoyancy studies and the results are presented in Table 8. The floating lag time ranged from 28 to 42 seconds. Among the formulations, F7 showed the shortest floating lag time (28 seconds), indicating rapid floating ability in the gastric medium. All formulations maintained buoyancy for more than 12 hours, demonstrating their suitability for prolonged gastric retention.

The optimized bilayer tablet formulation was evaluated for post-compressional parameters and the results are shown in Table 9. The hardness of the optimized tablets was found to be 5.9 ± 0.3 kg/cm², while friability was 0.785 ± 0.025%, indicating adequate mechanical strength and stability of the tablets. The tablets passed the weight variation test and showed a thickness of 5.3 ± 0.3 mm.

Drug content analysis of the optimized bilayer floating tablets was performed to determine the uniformity of drug distribution, and the results are presented in Table 10. The metformin content was found to be 99.45 ± 0.15%, while saxagliptin content was 98.78 ± 0.32%, indicating uniform distribution of both drugs within the bilayer tablet.

The dissolution study of the immediate release layer was conducted and the results are shown in Table 11. The instant layer released 96.65% of metformin within 15 minutes, indicating rapid drug release and confirming the effectiveness of the immediate release formulation.

The *in-vitro* dissolution profile of the floating sustained release layer was evaluated for 12 hours and the results are presented in Table 12. The drug release gradually increased over time, with 25.65% release at 0.5 hours and reaching 98.78% at 12 hours. This sustained drug release pattern indicates effective controlled release of saxagliptin from the floating matrix system, ensuring prolonged therapeutic action.

Table 1: Composition of Meformin fast dissolving tablets

Ingredients(mg)	Formulation code								
	IF1	IF2	IF3	IF4	IF5	IF6	IF7	IF8	IF9
Meformin	500	500	500	500	500	500	500	500	500
Sodium Starch glycolate	15	20	25	_	_	_	_	_	_
Croscarmellose sodium	_	_	_	15	20	25	_	_	_
Crospovidone	_	_	_	_	_	_	15	20	25
Microcrystalline cellulose	24	19	14	24	19	14	24	19	14
Talc	5	5	5	5	5	5	5	5	5
Magnesium stearate	6	6	6	6	6	6	6	6	6
Total weight	550	550	550	550	550	550	550	550	550

Table 2: Various formulations of gastro retentive floating tablet of Saxagliptin

Excipients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Saxagliptin	5	5	5	5	5	5	5	5	5
HPMC K 15	_	_	_	80	100	120	40	50	60
HPMC K 4	80	100	120	_	_	_	40	50	60
PVP K30	15	15	15	15	15	15	15	15	15
Citric acid	5	5	5	5	5	5	5	5	5
$NaHCO_3$	15	15	15	15	15	15	15	15	15
$Mg(C_{18}H_{35}O_2)_2$	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5
Lactose	70	50	30	70	50	30	70	50	30
Total Weight	200	200	200	200	200	200	200	200	200

Table 3: Results of pre-compressional parameters of Meformin

Formulation code	Parameters			
	Loose Bulk density(gm/ml)	Tapped bulk density(gm/ml)	Carr's Index (%)	Hausner's Ratio
IF1	0.345	0.452	23.673	1.310
IF2	0.335	0.456	26.535	1.361
IF3	0.348	0.453	23.179	1.302
IF4	0.352	0.463	23.974	1.315
IF5	0.351	0.461	23.861	1.313
IF6	0.347	0.459	24.401	1.323
IF7	0.342	0.458	25.328	1.339
IF8	0.346	0.463	25.270	1.338
IF9	0.348	0.457	23.851	1.313

Table 4: Results of post-compression parameters of all formulations

F. Code	Hardness test (kg/cm^2)	Friability (%)	Weight variation (%)	Thickness (mm)	Drug content (%)
IF1	3.2	0.612	Passes	3.4	97.78
IF2	3.1	0.589	Passes	3.3	98.12
IF3	3.3	0.557	Passes	3.4	98.74
IF4	3.2	0.569	Passes	3.4	98.65
IF5	3.2	0.574	Passes	3.6	97.12
IF6	3.1	0.563	Passes	3.5	96.65
IF7	3.3	0.574	Passes	3.6	99.45
IF8	3.2	0.652	Passes	3.5	97.15
IF9	3.2	0.745	Passes	3.7	98.32

Table 5: Results of disintegration time of all formulations

Formulation code	*In vitro* disintegration time (sec.) (n=3) Mean ± SD
IF1	95±5
IF2	93±3
IF3	97±2
IF4	68±4
IF5	62±8
IF6	55±3
IF7	40±5
IF8	62±2
IF9	55±3

Table 6: Result of pre-compression properties of Saxagliptin floating sustain release formulations

F. code	Bulk density(gm/ml)	Tapped density(gm/ml)	Compressibility index	Hausner ratio
F1	0.425	0.532	20.113	1.252
F2	0.432	0.542	20.295	1.255
F3	0.422	0.536	21.269	1.270
F4	0.415	0.521	20.345	1.255
F5	0.432	0.543	20.442	1.257
F6	0.415	0.536	22.575	1.292
F7	0.439	0.548	19.891	1.248
F8	0.441	0.556	20.683	1.261
F9	0.428	0.532	19.549	1.243

Table 7: Results of post compression of Saxagliptin floating sustain release Tablets

F. code	Thickness (mm)	Hardness (kg/cm^2)	Weight variation (mg)	Friability (%)	Drug content (%)	Total floating duration (h)
F1	3.4	5.2	205	0.665	97.85	>12
F2	3.5	5.3	200	0.568	98.82	>12
F3	3.6	5.4	198	0.685	98.54	>12
F4	3.4	5.2	203	0.752	98.65	>12
F5	3.5	5.2	196	0.732	98.65	>12
F6	3.3	5.3	198	0.652	99.05	>12
F7	3.4	5.4	193	0.662	99.85	>12
F8	3.5	5.5	197	0.674	98.82	>12
F9	3.4	5.6	205	0.745	98.78	>12

Table 8: Results of *In-vitro* buoyancy study of Saxagliptin floating sustain release tablets

Formulation Code	Floating lag times (sec)	Total Floating Time (hrs)
F1	42	>12
F2	38	>12
F3	32	>12
F4	36	>12
F5	32	>12
F6	38	>12
F7	28	>12
F8	36	>12
F9	39	>12

Table 9: Post-Compressional Parameters of Optimized Formulation

Formulation code	Hardness test (kg/cm^2)	Friability (%)	Weight variation	Thickness (mm)
1.	5.9±0.3	0.785±0.025	Pass	5.3±0.3

Table 10: Results of Drug content analysis

Formulation	Meformin	Saxagliptin
	(%) Label Claim	
In-house Bilayer floating tablet	99.45±0.15	98.78±0.32

Table 11: Results of dissolution rate studies of instant layer

Time (min)	% Drug Release of Instant layer
15	96.65 %

Table 12: Results of dissolution rate studies of floating layer

Time (Hour)	% Drug Release of floating layer
0.5	25.65
1	36.65
1.5	45.58
2	59.98
4	65.45
6	73.45
8	85.65
10	96.65
12	98.78

CONCLUSION

The present study successfully developed bilayer tablets of Metformin and Saxagliptin for the effective management of type 2 diabetes mellitus. The formulation showed satisfactory pre-compression and post-compression characteristics. The immediate release layer of Metformin provided rapid drug release, while the floating sustained release layer of Saxagliptin exhibited prolonged drug release for up to 12 hours. The optimized bilayer tablets demonstrated good mechanical strength, uniform drug content, and excellent floating behavior. The developed bilayer tablet system may improve therapeutic efficacy, provide sustained drug action, and enhance patient compliance.

DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

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