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FORMULATION AND EVALUATION OF BILAYER TABLET OF DAPAGLIFLOZIN AND VILDAGLIPTIN

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Abstract
Diabetes is a chronic illness that results from insufficient insulin production by the pancreas or from inefficient insulin usage by the body. Combination therapy employing two antidiabetic medications effectively manages these numerous problems. The creation of the bi-layer tablet, which combines several qualities with a controlled release formulation, is a new chapter in the successful delivery of medication. The goal of the current study was to create bi-layer tablets containing Dapagliflozin fast dissolving and Vildagliptin gastro retentive tablets. At first, about nine formulations of Dapagliflozin instant release tablets were prepared Result of pre compression parameter for these nine formulations were found to be within limits. The result of post compression parameter revealed that maximum drug content in formulation IF7 which is 99.45±0.26. Further about eight formulations of Vildagliptin tablets were prepared. The post compression properties of Vildagliptin tablets revealed that maximum drug content of 99.45±0.14 in F7 formulation. The post compression parameter of bilayer tablet was then performed. The hardness & friability was estimated to be 6.8 kg/cm^2 & 0.658 % respectively while the thickness was found to be 5.12mm. The drug content in bilayer tablet was observed to be 99.18% for Dapagliflozin and 99.45% for Vildagliptin. According to dissolution rate studies of bilayer tablets it was observed that within 1.5 hour the % drug release with respect to Dapagliflozin was 98.65% while for Vildagliptin it was 98.14% in 12 hours. The current investigation found that bilayer tablets containing Dapagliflozin and Vildagliptin may be a preferable option than standard dosage forms.

Keywords: Dapagliflozin and Vildagliptin, Diabetes, Bi layer tablet, Fast dissolving, Gastroretentive

Introduction

Diabetes is a chronic illness that results from insufficient insulin production by the pancreas or from inefficient insulin usage by the body. One hormone that aids in blood sugar regulation is insulin. Uncontrolled diabetes results in hyperglycemia, or elevated blood sugar, which over time damages numerous bodily systems, including blood vessels and neurons, catastrophically. In 2014, 8.5% of people over the age of 18 had diabetes. In 2019, diabetes was the primary cause of 1.5 million deaths, with 48% of these deaths happening in people under the age of 70. Between 2000 and 2016, the prevalence of premature mortality (death before the age of 70) increased by 5% due to diabetes. The illness known as type 2 diabetes mellitus is diverse and includes issues with the pancreatic β-

cell, liver, and peripheral tissues like adipose and skeletal muscle (Asmat *et al*., 2016; Padhi *et al*., 2020).

These multiple complications are well managed by combination therapy using two antidiabetic drugs. Combination therapy is more advantageous than monotherapy in minimizing problems such as dose-dependent side effects, dosing frequency, etc. A low-dose combination of two different drugs reduces dose-related risks and minimizes the clinical and metabolic side effects that occur with the maximal dosage of individual components as in monotherapy, and thus dosage of the single components can be reduced. Combination therapy employing two antidiabetic medications effectively manages these numerous problems. Combination therapy is superior to monotherapy in terms of reducing issues like dosage frequency, adverse effects that are depending on the dose, etc. The dosage of the individual components can be decreased because a low-dose combination of two different drugs minimizes the risks associated with dose and the clinical and metabolic side effects that can arise from using the maximal dosage of each drug in monotherapy. Diabetes requires a lot of attention since glucose levels, which rise after meals, must be maintained throughout the day for the body to function properly. Sustained-release (SR) formulations that control antidiabetic action continuously must be developed to maximize the postprandial rising of glucose levels in order to counteract such circumstances (Bailey and Day, 2003; Gimenes *et al*., 2009; Prabhakar *et al*., 2014).

The creation of the bi-layer tablet, which combines several qualities with a controlled release formulation, is a new chapter in the successful delivery of medication. With the use of bilayer tablet technology, two incompatible chemicals can be separated into two layers: a loading dose that is released immediately and a maintenance dose that is released gradually. A dose form with delayed release is intended to release the medication at a time other than right after it is administered. Using delayed release products is mostly done to shield the drug from gastric fluids, lessen gastric discomfort from pharmaceuticals that are very irritating to the stomach, or speed up gastrointestinal transit for medications that are better absorbed from the intestineEnteric-coated or colon-specific delayed release products are common. It is created by coating the medication solely in areas that fall within a particular pH range. It is created by applying a PH-sensitive polymer mixture to the drug-containing core (Yki-Järvinen, 2001; Panchal *et al*., 2012; Rameshwar *et al*., 2014).

The first sodium-glucose cotransporter 2 (SGLT2) inhibitor to receive approval was dapagliflozin. recommended for controlling type 2.3 diabetic mellitus Dapagliflozin improves glycemic management in adults when paired with diet and exercise because it causes glycosuria, which is the inhibition of glucose reabsorption in the proximal tubule of the nephron.1. Studies have looked into dapagliflozin as a stand-alone medication or in combination with other oral hypoglycemic medications like insulin (Deshpande *et al*., 2011; Plosker *et al*., 2014).

Vildagliptin is a dipeptidyl peptidase-4 (DPP-4) enzyme-specific inhibitor that is an oral active antihyperglycemic medication. In type II diabetes mellitus, where GLP-1 secretion and insulinotropic effects are compromised, it is employed as a management tool. The incretin hormones that stimulate insulin secretion and control blood glucose levels, glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are not broken down by vildagliptin because it inhibits DPP-4. Improved glycemic control is the direct consequence of elevated GLP-1 and GIP levels. Vildagliptin has a comparatively low risk of hypoglycemia in clinical trials (Dhillon, 2019; Keating, 2010; Halimi *et al*., 2010).

Thus this study deals with formulation and evaluation of Bilayer tablet of Dapagliflozin and Vildagliptin.

Materials & Methods

Chemicals

Sodium Starch glycolate, Croscarmellose sodium, Crospovidone, Microcrystalline cellulose, Talc, Magnesium stearate.

Formulation development

Preparation of instant layer of Dapagliflozin (Phase-1)

Fast dissolving (Instant Layer) tablets of Dapagliflozin were prepared by direct compression method after incorporating different super disintegrants such as, crosscarmellose sodium (Ac-Di-Sol), crospovidone and sodium starch glycolate in different concentrations.

Table 1: Composition of Dapagliflozin fast dissolving tablets

Ingredients (mg)	Formulation code								
	IF1	IF 2	IF 3	IF 4	IF 5	IF 6	IF 7	IF 8	IF 9
Dapagliflozin	10	10	10	10	10	10	10	10	10
Sodium Starch glycolate	10	15	20	-	-	-	-	-	-
Croscarmellose sodium	-	-	-	10	15	20	-	-	-
Crospovidone	-	-	-	-	-	-	10	15	20
Microcrystalline cellulose	65	60	55	65	60	55	65	60	55
Talc	5	5	5	5	5	5	5	5	5
Magnesium stearate	10	10	10	10	10	10	10	10	10
Total weight	100	100	100	100	100	100	100	100	100

Evaluation of Precompression Parameter

Bulk density: Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. Accurately weighed amount of granules taken in a 50 ml capacity measuring cylinder was tapped for 100 times on a plane hard wooden surface and estimated the LBD and TBD.

Losse bulk density was calculated by dividing mass of powder by volume of packing while tapped builk density was calculated by dividing mass of powder by Tapped volume of packing.

Carr's Compressibility index: Percent compressibility of powder mix was determined by Carr's compressibility index. It is the difference between Tapped & losse biulk density divided by Tapped bulk density multiplied by 100.

Hausners ratio: It is determined by dividing tapped bulk density by loose bulk density.

Evaluation of post compression Parameter

Shape and colour of tablets:

Uncoated tablets were examined under a lens for the shape of the tablet and colour was observed by keeping the tablets in light (Suresh *et al*., 2007).

Thickness test

Three tablets were picked from each formulation randomly and thickness was measured individually. It is expressed in mm and standard deviation was also calculated. The tablet thickness was measured using dial-caliper (Mitutoyo, Japan).

Weight variation test

Twenty tablets were selected randomly from each formulation and average weight was determined. The tablets were weighed individually and compared with average weight. The U.S Pharmacopoeia allows a little variation in the weight of a tablet. The following percentage deviation in weight variation is allowed.

Hardness test
The hardness of tablet was measured by Pfizer hardness tester and results were expressed in Kg/cm^2.

Friability test
For this, 20 tablets were taken from each formulation and the friability was determined using Roche friabilator. The equipment was run for 4min at 25 revolutions per minute. The tablets were taken out, dedusted and reweighted and % friability was calculated. The % friability was determined by dividing tapped bulk density by loss in weight divided by initial weight multiplied by 100 (Rane *et al*., 2012).

Uniformity of drug content:
The test is mandatory for tablets with 10mg or less weight of active ingredient. Ten randomly selected tablets from each formulation (F1 to F9) were finely powdered and Drug equivalent to 10 mg of drug dissolved in 10 ml 0.1 N HCl (Simulated gastric fluid of pH 1.2 without enzymes) sonicate it for 20 minutes, till the entire drug leached out from complex, then the solution was filtered through whatman filter paper No. 41. From this Solution take 1 ml and Diluted up to 100 ml with 0.1 N HCl and the drug content was determined spectrophotometrically at 232nm for Dapagliflozin.

Method for preparation of gastroretentive tablets of Vildagliptin
Direct compression was followed to manufacture the floating tablets of Vildagliptin. Eight different formulations (F1, F2, F3, F4, F5, F6, F7, & F8) were prepared by direct compression.

Table 2: various formulations of Vildagliptin gastro retentive tablets

Excipients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Vildagliptin	50	50	50	50	50	50	50	50
HPMC K4	90	120	-	-	-	-	30	40
HPMC K15	-	-	90	120	-	-	30	40
Xanthan gum	-	-	-	-	90	120	30	40
PVP K30	15	15	15	15	15	15	15	15
Talc	5	5	5	5	5	5	5	5
Magnesium Stearate	10	10	10	10	10	10	10	10
Lactose	80	50	80	50	80	50	80	50
Total Weight	250	250	250	250	250	250	250	250

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 (Hardikar and Bhosale, 2018).

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 reacts with dye and analyzed for drug content by UV spectrophotometer at a λ max of 210nm using of 0.1 N HCl as blank (Bomma *et al*., 2009).

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.

***In vitro* drug release study of gastro retentive tablet**
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±0.50ºc and rpm of 75. One Vildagliptin 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 (37^0C) 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 and take the absorbance at 210nm using spectroscopy (Raza *et al*., 2020).

Formulation development of bilayer tablet
Optimized formulation IF-7 of Instant release layer and optimized formulation of F-7 for control release used for formulation of Bi-layer tablet (Payghan and Disuza, 2011).

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 [100].
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 (Maddiboyina *et al*., 2020).

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 10mg of Vildagliptin was transferred to 10ml standard flask. The powder was dissolved in 10 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 0.2 ml to 10 ml suitably 10 ppm solutions of and determines the Conc. of drug at 210nm or Vildagliptin and 232nm for Dapagliflozin.

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 period for Vildagliptin and Dapagliflozin bilayer tablets 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. (Labindia 3000 plus) spectrophotometer (Bijank *et al*., 2013).

Results & Discussion

Vildagliptin and Dapagliflozin bilayer tablets were made with polymers such as Sodium Starch glycolate, Croscarmellose sodium, Crospovidone, HPMC K4, HPMC K15, Xanthan gum, PVP K30 for hypoglycemic therapy.

At first, about nine formulations of Dapagliflozin instant release tablets were prepared Result of pre compression parameter for these nine formulations suggest that loose bulk density varied from 0.341 to 0.365 gm/ml. Further tapped bulk density ranged from 0.452 to 0.474 gm/ml. The cars index extends form 22.996 to 24.947 while the hausner's ratio ranged between 1.299 to 1.332. The result of post compression parameter revealed that maximum drug content in formulation IF7 which is 99.45±0.26. The maximum 7 minimum thickness was noted in IF5 & IF3 which is 1.85±0.08 & 1.58±0.08 respectively. The friability ranged between 0.585±0.045 to 0.745±0.036% The results of hardness test ranged from 3.4±0.2 to 3.7±0.2 kg/cm^2. The disintegration time of instant layer of Dapagliflozin was found to be minimum with formulation IF7 which is 45±2.

Further about eight formulations of Vildagliptin tablets were prepared. The bulk density varied between 0.351 to 0.381 gm/ml. The tapped bulk density extends between 0.462 to 0.483 gm/ml. The maximum & minimum compressibility index found to be 24.026 to 22.561. The Hausner ratio varied from 1.291 to 1.316.

The post compression properties of Vildagliptin tablets revealed that maximum drug content of 99.45±0.14 in F7 formulation. The friability for F7 was noted to be 0.785±0.018 while the weight variation was estimated to be 249±6 which is least among all formulation. The thickness ranged between 3.2±0.3 to 3.5±0.2mm while the hardness extends from 5.6±0.2 to 5.4±0.1.

In-vitro drug release study of tablets revealed that maximum drug release of 98.78 was with F7 formulation. The post compression parameter of bilayer tablet was then performed. The hardness & friability was estimated to be 6.8 kg/cm^2 & 0.658 % respectively while the thickness was found to be 5.12mm. The drug content in bilayer tablet was observed to be 99.18% for Dapagliflozin and 99.45% for Vildagliptin. According to dissolution rate studies of bilayer tablets it was observed that within 1.5 hour the % drug release with respect to Dapagliflozin was 98.65% while for Vildagliptin it was 98.14% in 12 hours.

Table 3: Results of pre-compressional parameters of Dapagliflozin instant release tablets

Formulation code	Parameters			
	Loose Bulk density(gm/ml)	Tapped bulk density(gm/ml)	Carr's Index (%)	Hausner's Ratio
IF1	0.345	0.458	24.672	1.328
IF2	0.352	0.469	24.947	1.332
IF3	0.341	0.452	24.558	1.326
IF4	0.365	0.474	22.996	1.299
IF5	0.347	0.456	23.904	1.314
IF6	0.358	0.469	23.667	1.310
IF7	0.341	0.453	24.724	1.328
IF8	0.349	0.452	22.788	1.295
IF9	0.347	0.453	23.400	1.305

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	3.7±0.2	0.585±0.045	98±5	1.78±0.05	98.78±0.32
IF2	3.5±0.3	0.678±0.054	99±4	1.68±0.03	98.65±0.25
IF3	3.4±0.2	0.745±0.032	102±3	1.58±0.08	97.85±0.15
IF4	3.6±0.1	0.587±0.014	100±2	1.63±0.07	98.12±0.25
IF5	3.7±0.2	0.698±0.025	103±4	1.85±0.08	96.65±0.45
IF6	3.5±0.2	0.745±0.036	99±6	1.74±0.07	97.78±0.32
IF7	3.6±0.1	0.652±0.024	98±3	1.65±0.06	99.45±0.26
IF8	3.6±0.2	0.632±0.032	98±2	1.65±0.08	98.78±0.28
IF9	3.7±0.2	0.668±0.025	99±4	1.73±0.36	96.32±0.27

Table 5: Results of Disintegration time of instant layer of Dapagliflozin

Formulation code	Disintegration time (sec.) (n=3) Mean ± SD
IF1	65±5
IF2	72±3
IF3	69±4
IF4	78±5
IF5	65±6
IF6	69±3
IF7	45±2
IF8	71±4
IF9	69±5

Table 6: Result of pre-compression properties of Vildagliptin tablets

F. Code	Bulk density(gm/ml)	Tapped density(gm/ml)	Compressibility index	Hausner ratio
F1	0.375	0.485	22.680	1.293
F2	0.381	0.492	22.561	1.291
F3	0.358	0.467	23.340	1.304
F4	0.363	0.475	23.579	1.309
F5	0.371	0.483	23.188	1.302
F6	0.358	0.465	23.011	1.299
F7	0.362	0.471	23.142	1.301
F8	0.351	0.462	24.026	1.316

Table 7: Results of post compression properties of Vildagliptin tablets

F. code	Thickness (mm)	Hardness (kg/cm^2)	Weight variation (mg)	Friability (%)	Drug content (%)
F1	3.3±0.2	5.5±0.3	252±3	0.745±0.025	98.85±0.25
F2	3.2±0.3	5.6±0.2	250±5	0.658±0.032	97.74±0.36
F3	3.4±0.1	5.4±0.1	256±3	0.558±0.025	97.65±0.31
F4	3.5±0.2	5.4±0.2	254±2	0.569±0.021	98.36±0.25
F5	3.5±0.2	5.3±0.2	258±4	0.587±0.033	98.11±0.45
F6	3.3±0.3	5.4±0.3	248±5	0.658±0.011	97.85±0.28
F7	3.4±0.2	5.6±0.2	249±6	0.785±0.018	99.45±0.14
F8	3.5±0.3	5.4±0.2	252±4	0.658±0.017	96.65±0.36

Table 8: *In-vitro* drug release study of tablets

Time	% Cumulative Drug Release							
(hr)	F1	F2	F3	F4	F5	F6	F7	F8
0.5	53.32	46.65	42.25	40.23	35.65	32.25	28.85	25.45
1	69.98	62.23	53.32	56.65	52.23	49.98	36.65	35.65
1.5	86.65	79.98	69.98	69.98	68.85	63.32	49.98	49.98
2	98.98	89.98	78.85	83.32	74.45	78.85	57.74	53.32
3	99.14	99.05	83.32	94.45	89.98	83.32	69.98	64.47
4	-	-	98.85	99.05	93.32	89.69	79.98	76.65
6	-	-	-	-	99.05	93.32	83.32	82.23
8	-	-	-	-	-	98.74	93.32	91.15
12	-	-	-	-	-	-	98.78	94.74

Table 9: Post-compression parameters of optimized bilayer formulation

Formulation	Hardness test (kg/cm^2)	Friability (%)	Weight variation	Thickness (mm)
1.	6.8	0.658	Passes	5.12

Table 10: Results of Drug content analysis of bilayer tablets

Formulation	Dapagliflozin (% Label Claim)	Vildagliptin (% Label Claim)
In-house Bilayer tablet	99.18	99.45

Table 11: Results of Dissolution rate studies of bilayer tablets

Time (Hour)	% Drug Release	
	Dapagliflozin	Vildagliptin
0.5	46.65	23.32
1	72.23	35.58
1.5	98.65	45.65
2	-	53.32
4	-	68.87
6	-	74.45
8	-	89.98
10	-	96.65
12	-	98.14

Conclusion

The oral pharmaceutical bilayer tablet containing Vildagliptin and Dapagliflozin was successfully developed that can be used to administer therapeutically and prophylactically effective doses of anti-diabetic drugs. The goal is to achieve both a relatively quick onset of therapeutic effect and the maintenance of a therapeutically active plasma concentration for a considerable amount of time. The results of the experiment show that bi-layer tablets are effective at delivering the same medications in different ways. For example, one layer of the medication releases immediately to relieve pain quickly, and the second layer releases the medication gradually over time to increase its duration of action and decrease the need for repeated doses.

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