Journal of Animal Environment

(E-ISSN 2717-1396, ISSN 2717-1388)

Original Research Paper

NOVEL DRUG DELIVERY FOR SAXAGLIPTIN AND DAPAGLIFAZOLIN:A PARADIGM IN PHARMACEUTICAL RESEARCH

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Abstract:

The purpose of this study was to develop a gastro-retentive bilayer floating matrix tablet of saxagliptin HCL and dapagliflozin propanediol monohydrate. The tablet was successfully prepared using sodium starch glycolate for the immediate release layer and HPMC for the sustained release layer. All formulations of saxagliptin HCL and dapagliflozin propanediol monohydrate were prepared using wet granulation techniques. The main challenge was to design a bilayer floating matrix tablet with an initial loading dose, followed by a maintenance dose of up to 24 hours, while also prolonging the gastric residence time of the drug. The compatibility of saxagliptin HCL and dapagliflozin propanediol monohydrate and their physical mixture were confirmed using FTIR and DSC studies. The results from in vitro release studies showed that formulation SADBMF 1, containing 2% SSG and 30% HPMC, exhibited 99% release of saxagliptin HCL for 60 minutes and sustained release of dapagliflozin propanediol monohydrate for 24 hours. This formulation was considered optimized. It was observed that with increased concentrations of the polymers, the drug release profile was slower. The kinetics of in vitro drug release of the optimized formulation SADBMF1 were found to follow zero-order release kinetic models, and the drug release mechanism was identified as anomalous diffusion coupling with erosion.

Keywords: Saxagliptin HCL, Dapagliflozin propanediol monohydrate, bilayer floating matrix tablet, Immediate release, sustained release and In- vitro release.

1. Introduction:

Oral drug delivery has enlighten the patient compliance route for drug administration. Though it offers various advantages it has challenges like fluctuated drug release, narrow absorbtion window, stomach condition and drug stability in different pH environment throughout digestive tract. These challenges were minimized using gastroretentive drug delivery system (GDDS). This system found plethora of applications under one shade with increased retension time of drug, local delivery, reduced drug waste and importantly increased bioavailability. One of the GDDS, Floating tablet grabbed focus by not affecting motility of gastrointestinal tract (GIT) [1]. The bilayer tablet also found useful due to releasing two different drugs from two different layers at different or same rate. Numerous gastroretentive dosage forms are being developed and designed, such as: mucoadhesive systems that cause bioadhesion to the stomach mucosa, superporous hydrogel systems, floating systems by hot melt extrusion, low density floating systems that cause buoyancy in gastric fluid, floating osmotic pump, floating pulsatile delivery system, high density sinking systems that are retained at the bottom of the stomach, etc. In present research work gastroretentive dosage form for controlled release with improved bioavailability in upper part of stomach was prepared using antidiabetic drug [2-5]. Diabetes mellitus is one amongst the foremost common chronic diseases in nearly all countries, and continues to extend in numbers and significance as dynamical lifestyles cause reduced physical activity, and increased obesity. Diabetes causes death at about every 10 seconds and hence need a trustworthy treatment. The floating tablet maintain therapeutic level of drug by increasing the retention time [6]. Antidiabetic agents like biguanide derivatives, sulfonylurea, DPP-4 inhibitors, SGLT-2 inhibitors and meglitinide analogs are having a strong rationale for preparing gastroretentive dosage forms as they are absorbed from the upper part of gastrointestinal tract. Development of GRDDS of such drugs keeps the dosage form in the upper part of gastrointestinal tract and releases the drug in the sustained manner for the desired period.

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Received: 15th Jul, 2026 | Revised: 25th Jul, 2026 | Accepted: 5th Aug, 2026 | Available Online: 12th Aug, 2026

(DOI): 10.70102/AEJ.2026.18.3s.104

Literature supports the improved delivery of antidiabetic drugs, when gastric retention period is increased, leading to better control of the disease condition [7-10]. Hence, the present research was focused on preparing the gastroretentive bilayer floating tablet formulations of antidiabetic drugs to achieve better patient compliance and efficient treatment of type II diabetes mellitus [11]. Saxagliptin hydrochloride is a dipeptidyl peptidase-4(DPP-4) inhibitor used as an oral hypoglycaemic agent. It is used in combination with diet and exercise in the therapy of type 2 diabetes, either alone or in combination with other oral hypoglycemic agents. Saxagliptin hydrochloride is BCS class-III drug, being highly soluble and poorly permeable. Where, Dapagliflozin propanediol monohydrate is also indicated for the management of diabetes mellitus type-2 to improve glycemic control in adults when combined with diet and exercise. Dapagliflozin propanediol monohydrate is a sodium-glucose cotransporter-2 inhibitor, which prevents glucose reabsorption in the kidney. Combination therapy is mainly indicated as an adjunct to diet and exercise to improve glycemic control in adults with type-II Diabetes. Dapagliflozin propanediol monohydrate is BCS-III drug, being highly soluble and poorly permeable [12]. There are many previous estimates of the quantity of persons with diabetes disorder. The World Health Organization (WHO) printed estimates for the years 2000 and 2030, exploitation knowledge from forty countries however extrapolated to the 191 WHO member states. Other estimates are made by the International diabetes disorder Federation (IDF).The estimates produced here update the previous IDF estimates, and include all 216 countries of the United Nations [13-17]. Together, the DPP-4 and SGLT2 inhibitors fulfil a need for treatments with mechanisms of action that can be used in combination with a low risk of adverse events, such as hypoglycaemia or weight gain. Both classes have been reported to lower urinary albumin excretion, a risk factor for renal disease [18]. SGLT-2 in the proximal renal tubules is responsible for the majority of the reabsorption of filtered glucose. By inhibiting SGLT-2, Dapagliflozin propendiol monohydrate reduces reabsorption of filtered glucose and thereby increases urinary glucose excretion. As a competitive DPP-4 inhibitor, Saxagliptin hydrochloride slows the inactivation of the incretin hormones, thereby reducing fasting and postprandial glucose concentrations in a glucose-dependent manner in patients with T2DM [19-20]. It is also notable that, the GRDDS provides a new and important therapeutic option for delivery of anti-diabetic drug as they not only prolong dosing intervals, but also increase patient compliance as compared toexisting conventional and other controlled release dosage forms. The aim of the present work was to formulate and evaluate the gastroretentive bilayer floating matrix drug delivery system of antidiabetic drugs in order to increase their retention in stomach, which ultimately results in the increase of bioavailability along with extended duration of action resulting in possible reduction in dose, less side effects, low overall cost of therapy and hence better patient compliance.

2. Material and methods:

2.1 Material

Saxagliptin hydrochloride and Dapagliflozin propendiol monohydrate obtained as a gift sample from Morpen laboratories limited , HPMC K4M, K100M was gifted from Signet Chemical Corporation, Mumbai,Sodium starch glycolate,Croscarmellose sodium and Microcrystalline cellulose PH 101 was gifted from Arihant Innochem Pvt.Ltd, Mumbai, Sodium bicarbonate, magnesium stearate was gifted from Merck Pvt.Ltd. Mumbai, crosspovidone, lactose monohydrate, Citric acid, and Polyvinyl pyrrolidine K30 and isopropyl alcohol was purchased from Vishal Chemicals, Mumbai. All the chemicals and reagents required for the present experimental work are of analytical grade.

2.2 Methods

2.2.1 Preparation of immediate release tablets layer: For the preparation of immediate release layer various superdisintegrants were studied depending upon their tablet disintegration time and compatibility of drug with superdisintrgarant. Tablet containing 5mg of Saxagliptin HCL in immediate release layer were prepared by wet granulation method and various formulae used in the study are shown in the table No. 1.

2.2.2 Preparation of sustained release layer: For the preparation of sustained release layer various polymers were studies depending upon their swelling and gelling properties and its compatibility with drugs. Tablet containing 10mg of Dapagliflozin Propanediol Monohydrate were prepared by wet granulation method and various formulae used in the study are shown in the table No. 1.

3 Table 1: Composition of Immediate and sustained release layer tablet (SADBM F1- SADBM F8)

	Ingredients (mg)	SADBM F1	SADBM F2	SADBM F3	SADBM F4	SADBM F5	SADBM F6	SADBM F7	SADBM F8
IMM	Saxagliptin	5	5	5	5	5	5	5	5

IMMEDIATE LAYER	HCL								
	MCC PH 101	25	25	25	25	25	25	25	25
	Lactose Monohydrate	98.55	98.55	98.55	98.55	98.55	98.55	98.55	98.55
	PVP K30	15	15	15	15	15	15	15	15
	SSG	3	3	3	3	3	3	3	3
	Ferric Oxide	0.45	0.45	0.45	0.45	0.45	0.45	0.45	0.45
	IPA	qs	qs	qs	qs	qs	qs	qs	Qs
	Mg. Stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
	Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
	Total Weight	150	150	150	150	150	150	150	150
SUSTAINED LAYER	Dapagliflozin Propanediol Monohydrate	10	10	10	10	10	10	10	10
	HPMCK100	150 (30%)	125 (25%)	100 (20%)	50 (10%)	-	-	-	-
	HPMCK4M	-	-	-	-	150 (30%)	125 (25%)	100 (20%)	50 (10%)
	MCC PH101	220	245	270	320	220	245	270	320
	Sodium Bicarbonate	50	50	50	50	50	50	50	50
	Citric Acid	10	10	10	10	10	10	10	10
	PVP K30	50	50	50	50	50	50	50	50
	Mg. Stearate	5	5	5	5	5	5	5	5
	Talc	5	5	5	5	5	5	5	5
	Total Weight	500	500	500	500	500	500	500	500

3.1.1 Compression of bilayer tablet: In the present study bilayer tablet was prepared manually using 10 station punching machine. Accurately weighed amount of SR powder mixture was fed manually into die cavity. SR layer was compressed at mild compression force (5-6 kg/cm^2). After that accurately weighed IR powder was manually fed into die on SR layer and compressed using 12mm punches. Both the layer was identified on the basis of colour. The tablet were evaluated for appearance, weight variation, hardness, friability, thickness, swelling index, disintegration, adhesion test and In-vitro drug release. All the tablets were stored in airtight packages for further study. The tablet were evaluated for appearance, weight variation, hardness, friability, thickness, swelling index, disintegration, adhesion test drug content and In-vitro drug release [21].

3. Evaluation

3.1 Preformulation study

3.1.1 Solubility study Saxagliptin HCL and Dapagliflozin propanediol monohydrate Saturated solution of both the drugs was prepared in 0.1N HCL (pH 1.2) and 6.8pH phosphate buffer. Then vials were shaked at 37°C for 24 hours in mechanical shaker. After 24 hrs the medium was filtered using Whatman filter paper and analyzed by UV visible spectrophotometer. Then solubility of drugs in mcg/ml in specific medium was calculated by using formula[22]

$$\text{Amount dissolved}\left(\frac{\text{mg}}{\text{ml}}\right) = [\text{aborbance} - \text{intercept}]/\text{slope} \times \text{dilution factor} /1000 \times \text{bath volume}$$

3.1.2 Melting point determination: The melting point was determined by capillary method by using the melting point apparatus drug was filled in the glass tube which was sealed at one end that was attached with the thermometer. The drug containing capillary with

thermometer was dipped in liquid paraffin and progress in temperature was monitored. Inside the melting point apparatus temperature at which drug starts melting was recorded [23,25].

3.1.3 Compatibility study

3.1.3.1 FTIR study: IR spectroscopy was used to determine the molecular interaction between polymer and drugs. All physical mixtures and drugs sample were mixed with dried KBR in ratio 1:1. Then small fraction of mixtures was compressed on automatic IR Press at pressure 10 tones to form transparent pellet. Then the IR spectrum of pellets was taken on FTIR spectrophotometer [24,26].

3.1.3.2 DIFFERENTIAL SCANNING COLORIMETRY (DSC) study: Physical mixtures of drugs and polymers were filled in the prewashed, dried ampoules and sealed. The sealed ampoules were stored at 37 ± 0.5ºC for 28 days in stability chamber. At the end of 28 days ampoules were removed from stability chamber and subjected for interaction study. Drug polymer interaction study was carried out by using DSC. In this study thermogram of mixtures of Saxagliptin HCL and Dapagliflozin propanediol monohydrate, HPMCK4M, HPMCK100 was taken. Heating was done at a scan rate of 10°C/min [27].

3.1.3.3 UV analysis

3.1.3.3.1 PREPARATION OF CALIBRATION CURVE CALIBRATION CURVE IN 0.1N HCL (1.2pH): Preparation of calibration curve Calibration curve for Saxagliptin hydrochloride and Dapagliflozin propanediol monohydrate consisted of different concentration of standard Saxagliptin hydrochloride solution ranging from 2-14 µg/ml and Dapagliflozin propanediol monohydrate solution ranging from 2.5-25 µg/ml. These concentrations were prepared by pipetting out appropriate volumes of aliquots from the stock solution and dilute with 0.1N HCL (1.2pH) in 10 ml volumetric flask. The final volume was adjusted to 10 ml with the help of 0.1N HCL (1.2pH). Absorbance of the all solutions were taken at 213 nm and 224 nm against the blank solution prepared in the same manner without adding the drug. The absorbance differences of resulting solutions were plotted against their respective concentration [28,29].

3.1.3.3.2 PREPARATION OF CALIBRATION CURVE CALIBRATION CURVE IN pH6.8 PHOSPHATE BUFFER: Preparation of calibration curve Calibration curve for Saxagliptin hydrochloride and Dapagliflozin propanediol monohydrate consisted of different concentration of standard Saxagliptin hydrochloride solution ranging from 2-18 µg/ml and Dapagliflozinpropanediol monohydrate solution ranging from 2.5-25 µg/ml. These concentrations were prepared by pipetting out appropriate volumes of aliquots from the stock solution and dilute with 6.8 pH phosphate buffer in 10 ml volumetric flask. The final volume was adjusted to 10 ml with the help of 6.8 pH phosphate buffer. Absorbance of the all solutions were taken at 213.20 nm and 222.40 nm against the blank solution prepared in the same manner without adding the drug. The absorbance differences of resulting solutions were plotted against their respective concentration [30-32].

3.1.4 Formulation parameters:

3.1.4.1 Precompression study [33-36]

3.1.4.1.1 Angle of repose The angle of repose was determined by the funnel method. The accurately weighed powder was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powder. The powder was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured. The angle of repose was calculated by using the following equation.

$$\tan(\theta) = h/r$$

Where ‘h’ and ‘r’ are the height and radius respectively of the powder cone

3.1.4.1.2 Bulk density: It is the ratio of powder to the bulk volume of powder. It was measured by pouring the weighed powder (passed through standard sieve #20) into a measuring cylinder and initial weight was noted. This initial volume was called the bulk volume. From this bulk density was calculated according to the formula mentioned below. It is expressed in gm/ml.Determination of bulk density of powder was determined by pouring gently 10gm of sample through a glass funnel into a 50ml graduated cylinder. The volume occupied by the sample was recorded. The bulk density was calculated as follows:

$$\text{Bulk Density} = \text{Wt. of Powder in grams} / \text{Bulk Volume}$$

Tapped density:

Determination of tapped bulk density accurately weighed 10gm of drug was taken, previously passed through 20 # sieve and was transferred in 50 ml graduated cylinder. Then the cylinder was mechanically tapped containing the sample by raising and allowing it to drop under its own weight using mechanically tapped density tester that provides a fixed drop of 14 ± 2 mm at a nominal rate of 300 drops per minute. The cylinder was tapped for 500 times initially and measured the tapped volume (V1) to the nearest graduated units, repeated the tapping an additional 750 times and measured the tapped volume (V2) to the nearest graduated units. If, the difference between the two volumes is found to be less than 2% then, final the volume (V2) was taken.

$$Tapped\ Density = Wt. Powder\ in\ grams / Tapped\ Volume$$

3.1.4.1.3 Compressibilty index: The compressibility index of all ingredients were determined by following equation

$$Carr's\ Index = [(TD - BD)\ x\ 100 / TD]$$

3.1.4.1.4 Hausner's ratio

Hausner's ratio was determined by measuring both bulk density and tapped density of powder. It is determined by the following equation:

$$Hausner's\ ratio = TD/LD$$

3.1.4.2 Post Compression evaluation

3.1.4.2.1 Thickness and diameter: Thickness and diameter of tablets were accurately measured by using Vernier calliper for desired uniformity in size and shape.

3.1.4.2.2 Hardness: Tablet requires certain amount of strength or hardness which was measured by Monsanto hardness tester. Ten tablets were randomly picked from each formulation and were subjected for relative hardness and the value was expressed in Kg/cm^2.

3.1.4.2.3 Friability : The 10 tablets were subjected to the test of friability with initial weight (Wi) of the tablets is noted. The tablets were allowed to fall on it from a height of 6 inches while the friabilator drum was rotated for 100 times at 25 rpm for 4 minutes. The final weight (Wf) of the tablets after subjecting to friability was noted and the friability was calculated according to the formula.

$$Friability\ (\%) = (Initial\ weight - Final\ weight)/Initial\ weight * 100$$

3.1.4.2.4 Disintegration test: Six tablets were selected randomly from each batch for the disintegration test (DBK TABLET DISINTEGRATION). Disintegration test was performed in 0.1N HCL for 15min and remaining was carried out in 6.8 ph phosphate buffer using Disintegration tester (USP). Disintegration time (DT) was measured for immediate release layer tablets and also for bilayer tablets [37-38].

3.1.4.2.5 Drug Content: 20 tablets were accurately weighed and powdered. Then powder equivalent to 5mg of Saxagliptin HCL and 10mg 0f Dapaglflizon propanediol monohydrate was shaken vigorously with 20 ml of 0.1N hydrochloric acid (ph 1.2) and phosphate buffer pH 6.8 for 10 min and added sufficient 0.1N hydrochloric acid (ph 1.2) and phosphate buffer pH6.8 to produce 50 ml and filtered. Each ml of filtrate was suitably diluted to 10 ml 0.1N HCL (ph 1.2) and phosphate

buffer pH6.8. The absorbance of resulting solution was measured at maximum 213 and 222.40 nm. From the absorbance the drug content of the tablets was calculated [39].

3.1.4.2.6 Weight variation: Twenty tablets were selected randomly and weighed individually. Average weight was calculated and compared the individual tablet weight to the average weight.

3.1.4.2.7 Wetting study and water absorption ratio for immediate release formulation: Twice folded tissue paper was placed in a Petri dish having an internal diameter of 5 cm containing 6 ml of 0.1N HCl (pH 1.2). A tablet was carefully placed on the surface of the tissue paper in the Petri dish. The time required for water to reach the upper surface of the tablet and to completely wet was noted as the wetting time and change in weight is noted as water absorption ration and calculated by formula: $R = Wa - Wb \times 100$, Where Wb represents initial weight of tablet and Wa represents final weight of the tablet.

3.1.4.2.8 *In vitro* buoyancy studies: The floating behaviour of the tablets was visually determined, in triplicate, according to the floating lag time method. Briefly, a tablet was placed in a glass beaker, containing 200 ml of 0.1 N HCl, maintained in a water bath at 37 ± 0.5 ºC. The floating lag time, ‘‘the time between tablet was placed in a glass beaker with 0.1N HCl and its buoyancy” and total floating duration, ‘‘the time during which tablet remains buoyant”, were recorded.

3.1.4.2.9 *In-vitro* dissolution study: In vitro drug release study was performed using type I (Basket) apparatus (DBK-, Dissolution rate test apparatus USP Mumbai, India) at 50 rpm in 900 ml 0.1N HCL 1.2 pH for 1hr temperature was maintained at 37 ± 0.5^{0}C and phosphate buffer ph 6.8 maintained at 37 ± 0.5^o C. The test was subjected for 24 hrs, each tablet was placed in 0.1N HCL for 1hrs and it is placed the phosphate buffer pH 6.8. The 10ml sample was withdrawn at specified time intervals, diluted with 0.1N HCL and phosphate buffer pH 6.8, and replaced with same fresh dissolution media to maintain sink condition. The withdrawn samples were filtered through membrane filter 0.45µm, suitably diluted and analyzed by using UV spectrophotometer (UV shimadzu) at λmax 213nm and 222.40nm. This test was performed on 3 tablets and mean ± SD was calculated. The release of the prepared gastroretentive formulations was compared with the theoretical r release of the drug using model independent method by calculating similarity and dissimilarity factor [40].

3.1.4.2.10 Stability study: The purpose of stability testing is to provide evidence on how the quality of the drug substance or drug product varies under the influence of a variety of environmental factors such as temperature, light and humidity, enabling suggested storage conditions, retest periods and shelf lives . Storage condition according to ICH guidelines for stability studies Study Storage condition Minimum time period required Long term* 25^{0}C±2^{0}C/60%RH±5% RH or 30^{0}C±2^{0}C/65%RH±5% RH 12 months Intermediate** 30^{0}C±2^{0}C/65%RH±5% RH 6 months Accelerated 40^{0}C ± 2^{0}C/75% RH ± 5% RH 6 months. The accelerated condition that was chosen for stability study was 40^{o}C ± 2^{o}C/ 75% ± 5% RH (Climatic zone III condition for accelerated testing) and sample were withdrawn after 0,1,3 months.

RESULTS and DISCUSSIONS:

i. Preformulation study:

a) Solubility study: The solubility of both drugs were checked in 1.2 pH HCl and 6.8 phosphate buffer system. The results obtained were given in table 2.

Table 2 : Solubility study of API in different pH system

Medium	Solubility (mg/ml)	
	1.2 pH HCl	6.8 pH phospha

Active constituent		te buffer
Saxagliptin HCl	21.68889±0.356423	15.28682± 0.008951
Dapagliflozin propanediol monohydrate	20.84848±0.160349	19.87097± 0.193548

b) Melting point determination: The identification of standard drug has been carried out by melting point study. The melting point of drug Saxagliptin Hydrochloride and Dapagliflozin Prpanediol Monohydrate are given in table 3.The melting point study shows that the drug is within standard limits of melting point.

Table 3: Melting point data

Drug	Reported melting point (^{0}C)	Observed melting point (^{0}C)
Saxagliptin hydrochloride	205-207	204-206
Dapagliflozin propanediol monohydrate	74-78	75-78

c) Compatibility study

a. FTIR study: The FTIR spectra of pure drug Saxagliptin HCL, Dapagliflozin propanediol monohydrate, HPMCK100, HMPCK4M, SSG, CCS (AC-Di-Sol), Crosspovidone (Polyplasodone XL) and other excipients mixture used for immediate release layer and sustained release layer in optimized formulation were obtained and these shown in figure1.

b. DSC study: The DSC spectra of pure drug Saxagliptin HCL, Dapagliflozin propanediol monohydrate and mixture of Dapagliflozin propanediol monohydrate and HPMC K100, Dapagliflozin propanediol monohydrate and HMPC K4M.

c. UV analysis: The solution of Saxagliptin hydrochloride and Dapagliflozin propanediol monohydrate in 0.1N HCL (pH1.2) and phosphate buffer (6.8 pH) were scanned in the range of 200-400nm for determination of wavelength.

ii. Formulation study:

a) Precompression study:

The pre-compression study (Table No. 4) shows that all the batches are flowable from data of Bulk density, tapped density, angle of repose, Carr's index, and Hausner's ratio.

Table 4: Precompression study of batches SIRF1 to SIRF12 and SADBMF1 to SADBMF8

F.CODE	Bulk density (g/cc)	Tapped density (g/cc)	Angle of repose ($^\theta$)	Carr's index (%)	Hausner's ratio	Flow rate
SIRF 1	0.376± 0.027	0.415± 0.019	20.1± 1.83	9.34	1.10	Flowable
SIRF 2	0.438± 0.017	0.495± 0.038	19.53 ±2.89	11.21	1.13	Flowable
SIRF 3	0.434± 0.040	0.493± 0.030	17.51 ±2.07	11.96	1.13	Flowable
SIRF 4	0.593± 0.040	0.701± 0.052	19.24 ±0.91	15.21	1.18	Flowable
SIRF 5	0.56±0.11	0.68±0.099	16.97 ±4.14	17.85	1.2	Flowable
SIRF 6	0.496± 0.071	0.582± 0.098	16.98 ±1.95	14.53	1.17	Flowable
SIRF 7	0.348± 0.029	0.38±0.035	18.14 ±1.44	8.37	1.09	Flowable
SIRF 8	0.401± 0.040	0.44±0.049	14.74 ±1.31	10.08	1.11	Flowable
SIRF 9	0.358± 0.028	0.434± 0.037	15.9± 0.55	17.24	1.21	Flowable
SIRF 10	0.392± 0.021	0.453± 0.050	14.72 ±0.09	13.03	1.15	Flowable
SIRF 11	0.380± 0.023	0.441± 0.029	16.65 ±1.66	13.66	1.16	Flowable
SIRF 12	0.365± 0.016	0.448± 0.024	16.82 ±1.65	18.37	1.22	Flowable

SADBMF1	0.320±0.006	0.363±0.0051	18.61±0.901	11.74	1.13	Flowable
SADBMF2	0.283±0.0034	0.325±0.0046	18.63±1.24	12.48	1.14	Flowable
SADBMF3	0.251±0.0028	0.298±0.0046	17.69±0.301	14.71	1.17	Flowable
SADBMF4	0.251±0.0028	0.302±0.0046	17.39±0.416	16.84	1.20	Flowable
SADBMF5	0.298±0.0046	0.316±0.0085	19.31±1.438	5.76	1.06	Flowable
SADBMF6	0.259±0.0028	0.315±0.008	19.61±2.66	17.63	1.21	Flowable
SADBMF7	0.269±0.0075	0.306±0.0057	20.27±2.43	11.63	1.113	Flowable

iii. Post Compression evaluation

The post-compression study(table 4 and 5) like hardness, thickness, weight variation, and friability performed average result of each parameter was found within range.

Table 5: Post-compression study of batches SIRF1 to SIRF12 and SIRF1 to SIRF12 and SADBMF1 to SADBMF8

F.CODE	Average hardness (kg/cm^2)	Average weight variation (%)	Average friability (% W/W)	Average thickness (cm)	Drug content (%)	Disintegration time (sec)	Wetting time (sec)
SIRF1	3.33±0.288	0.82±0.44	0.35±0.05	0.237±0.0057	108.61±0.01	360±1.122	168±0.43
SIRF2	4±0.5	0.86±0.801	0.58±0.02	0.237±0.0057	98.055±0.00	342±1.093	132±0.62
SIRF3	4.23±0.25	0.46±0.47	0.62±0.06	0.233±0.0057	104.44±0.02	306±0.952	114±0.54
SIRF4	3.16±0.288	0.76±0.74	0.66±0.08	0.233±0.0057	98.055±0.001	218±1.264	89±0.61
SIRF5	3.56±0.11	0.62±0.68	0.42±0.02	0.23±0.01	96.11±0.01	128±0.785	98±0.60
SIRF6	4.83±0.288	0.66±0.64	0.66±0.05	0.233±0.0057	97.77±0.01	74±0.921	60±0.25
SIRF7	5.33±0.288	0.96±0.51	0.78±0.03	0.237±0.0057	91.94±0.00	59±0.654	32±0.36
SIRF8	5.16±0.288	0.86±0.86	0.80±0.05	0.237±0.0057	93.33±0.01	242±0.823	28±0.42
SIRF9	3.16±02 88	0.46±1.08	0.53±0.07	0.233±0.0057	98.055±0.01	126±0.882	89±0.32
SIRF10	5.33±0.288	0.82±0.444	0.68±0.02	0.233±0.0057	96.11±0.02	66±0.943	76±0.37
SIRF11	4.33±0.288	0.79±0.41	0.75±0.06	0.237±0.0057	112.5±0.03	48±0.943	44±0.36
SIRF12	5.166±0.288	0.72±0.71	0.78±0.08	0.237±0.0057	111.94±0.03	56±0.724	35±0.62
SADBMF1	6.16±0.288	0.17±0.911	0.57±0.071	0.526±0.0057	99.98±0.008	33±0.64	24.01±0.625
SADBMF2	5.66±0.288	0.10±0.804	0.49±0.093	0.523±0.0057	97.325±0.01	56±0.62	19.90±0.533
SADBMF3	6.16±0.288	0.22±1.039	0.61±0.054	0.526±0.0057	109.29±0.07	56±0.92	11.33±1.10
SADBMF4	6.5±0.5	0.01±1.25	0.58±0.085	0.526±0.0057	97.13±0.017	53±0.71	7.88±0.59
SADBMF5	5.83±0.288	0.15±1.10	0.63±0.056	0.53±0.01	100.76±0.005	32±0.62	6.66±0.723
SADBMF6	6.5±0.5	0.15±1.105	0.64±0.062	0.526±0.0057	73.93±0.005	25±0.82	10±0.614
SADBMF7	5.5±0.5	0.25±1.031	0.51±0.073	0.526±0.0057	108.40±0.04	24±0.67	15.61±0.520
SADBMF8	5.67±0.288	0.23±0.695	0.47±0.084	0.523±0.0057	96.75±0.01	25±0.72	19.94±0.68

a) *In vitro* buoyancy studies

The sodium bicarbonate and citric acid was added as a gas Generating agent to promote the floating capacity of tablet and the formulations containing More than 10% of sodium

bicarbonate and 2% citric acid had floating lag time less than 30 Seconds and floating duration more than 24 hours. From the swelling studies it was revealed That, as the concentration of hydrophilic polymer (HPMC) increased in floating matrix Tablets.

Table 6: Buyancy study of batches SADBMF1 to SADBMF8.

F.CODE	Floating lag time(sec)	Floating duration(hrs)
SADBMF1	33±0.64	24.01±0.625
SADBMF2	56±0.62	19.90±0.533
SADBMF3	56±0.92	11.33±1.10
SADBMF4	53±0.71	7.88±0.59
SADBMF5	32±0.62	6.66±0.723
SADBMF6	25±0.82	10±0.614
SADBMF7	24±0.67	15.61±0.520
SADBMF8	25±0.72	19.94±0.68

b) *In-vitro* dissolution study: For all formulations of Saxagliptin HCL and Dapagliflozin propanediol monohydrate bilayer sustained release matrix tablet, the dissolution profile is presented below. The graph plotted between %CDR (Y-axis) with respect totime (X-axis) and these are presented in figure 1& 2. From in vitro release studies, formulation SADBMF1containing 2% SSG and 30% HPMC K100M and showed release of Saxagliptin HCL 99% for 60 min and Dapagliflozin propanediol monohydrate with sustained drug release for 24hours (99%) emerged as optimized formulation.

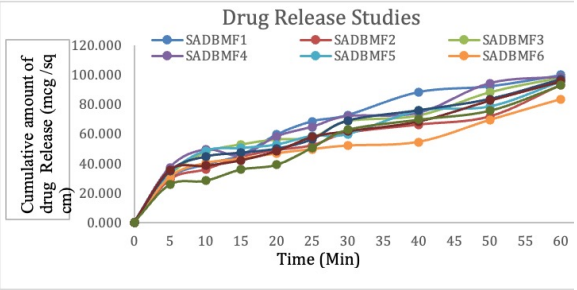


Fig 1: In Vitro Dissolution Studies Of SADBMF1-SADBMF8 in 0.1n HCl

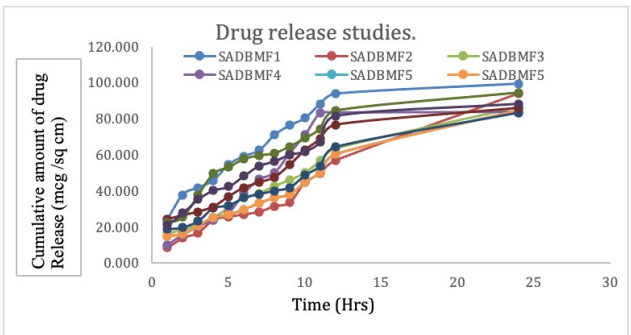


Fig. 2: In Vitro Dissolution Studies of SADBMF1-SADBMF8 in 6.8pH Phosphate Buffer

DISCUSSIONS:

All pre-compression parameters for each batch were evaluated, including the angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio. Post-compression parameters were also assessed, which included appearance, weight variation, thickness, hardness, friability, disintegration time, drug content, floating rate, floating time, water absorption, and in vitro dissolution studies. The batches were optimized based on the in vitro release study data.The formulation SADBMF1, which contained 2% SSG and 30% HPMCK100M, demonstrated a 99% release of Saxagliptin HCL within 60 minutes. Meanwhile, Dapagliflozin propanediol monohydrate exhibited a sustained drug release of 99% over 24 hours, confirming it as the optimized formulation. An increase in the concentration of the polymers resulted in a slower drug release profile.

Overall, the current study indicates that the Saxagliptin HCL and Dapagliflozin propanediol monohydrate gastroretentive bilayer floating matrix tablet shows promising potential as novel delivery dosage form.

CONCLUSION

The present research was carried out to develop a Gastroretentive bilayer floating matrix tablet of Saxagliptin HCL and Dapagliflozin propanediol monohydrate was prepared successfully by using sodium starch glycolate for immediate release and HPMC K100 for sustained release layer. All the formulation of Saxagliptin HCL and Dapagliflozin propanediol monohydrate i.e. Immediate release layer and Sustained release layer were prepared by wet granulation techniques. All the pre-compression parameter of all the batches were evaluated such as angle of repose, bulk density, tapped density, Carr's index and hausner's ratio. The post- compression parameter such as appearance, weight variation, thickness, hardness, friability, disintegration time, drug content, floating rate and floating time, water absorption and in-vitro dissolution studies were performed.

Thus the result of the current study clearly indicated that the Saxagliptin HCL and Dapagliflozin propanediol monohydrate gastroretentive bilayer floating matrix tablet under present investigation has a promising potential as a dosage form and can be used as an alternative to available marketed conventional dosage form as it released an initial loading dose that can be useful for immediate release and maintenance dose can be useful for prolong or sustained release for better therapeutic benefits to control diabetes mellitus. Also the formulation was found to be stable.

ACKNOWLEDGEMENT

The author wishes to thanks Mr. Avinash Aggarwal of Morepen Laboratories Limited, Mr. Nitin Kulkarni and Shrikant P Bellikatti of Lab India Analytical Instrument, Arihant Innochem Pvt.Ltd, and Merck Pvt.Ltd.

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