ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Design and Development of Immediate and Sustained Release Tablets of Vildagliptin.

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ABSTRACT

In this study immediate release and sustained release tablets of Vildagliptin was developed. Pharmabrust was used as super disintegrating agent in increasing order in immediate release formulations and methocel k4M CR as rate retarding polymer in sustained release formulations. Tablets were formulated by direct compression method. The *in-vitro* release profile were determined using USP I apparatus. The release profile of immediate release tablet of all the formulations was 95-100% within 45 minutes. The release profile of sustained release FS-1, FS-2, FS-3, FS-4, FS-5, FS-6 and FS-7 was 94%, 99%, 72%, 76%, 65% and 74% within 8 hours. Formulated tablets were evaluated for physical parameters such as average weight, thickness, disintegration time, potency, LBD, TBD, compressibility Index and angle of repose. All the physical properties of prepared tablets were within limit. Zero order, First order, Higuchi and Korsmeyer et al. models were used to estimate the kinetics of drug release. It was found that the release followed First order release kinetics, as the correlation coefficient R^2 value was higher for first order i.e. 0.995. Formulation 6 of immediate release tablet (FI-6) seems to be best similar to the innovator brand for higher f2 i.e. 51.6 and lower f1 value i.e. 3. Formulations were characterized by Fourier transform infrared (FTIR). No any chemical interaction was observed between excipients and drug from IR spectrum.

Keywords: Vildagliptin, immediate release, sustained release, pharmabrust, methocel k4M CR, *in-vitro* study.

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ISSN: 0975-8585

INTRODUCTION

Type 2 diabetes mellitus is a growing problem in most parts of the world. There is now good evidence that controlling hyperglycaemia can help prevent many of the serious complications associated with the disease [1]. Current drugs used for managing TYPE II Diabetes and its precursor syndromes, such as insulin resistance, fall into different classes of compound such as the biguanides, thiazolidinediones, the sulfonylureas peptide analogus, dipeptidyl Peptidase-IV inhibitors and alpha glucosidase inhibitors [2]. Among the most promising new classes of drugs for type 2 diabetes are those that leverage the incretin hormone glucagon-like peptide-1 (GLP-1) [1]. Vildagliptin is an oral anti diabetic drug from the peptide analogues (DPP-4 inhibitor class).Vildagliptin can be given in monotherapy as well as in combination with other antidiabetic drugs. It rapidly and completely inhibits the activity of DPP- 4 enzymes this results in increase of the two incretin hormones available in our body, they are glucose-like peptide-1(GLP-1) and glucose dependent insulinotropic peptide (GIP). The activation of these two hormones results in decrease of the blood glucose level by decreasing the glucagon secretion and increase of insulin sensitivity. GLP-1 activation enhances the β-cell sensitivity and reduces the α-cell sensitivity which results in increase in amount of insulin and decreases the amount of glucagon and reduces the glucose level in blood [6].

Sustained-release oral delivery systems are designed to achieve therapeutically effective concentrations of drug in the systemic circulation over an extended period of time, thus achieving better patient compliance and allowing a reduction of both the total dose of drug administered and the incidence of adverse side effects [3]. In long-term therapy, for the treatment of chronic disease conditions, conventional formulations are required to be administered in multiple doses and therefore have several disadvantages [4]. Matrix devices, due to their chemical inertness, drug embedding ability and drug release character, have gained steady popularity for sustaining the release of a drug [5].

The literature survey shows that there is no any published paper on discriminating dissolution study of Vildagliptin tablets and there is no any information about dissolution medium and λmax value of Vildagliptin in BP and USP for in-vitro. So we conducted the discriminating dissolution study for the selection of appropriate dissolution medium and suitable λmax. The purpose of this work is to design the immediate and sustained release tablets of Vildagliptin. To formulate immediate release tablets polymer pharmabrust was used in increasing amount from FI-1 to FI-7 formulations and polymer methocel k4M CR at increasing order were used to formulate sustained release tablets FS-1 to Fs-7 formulations. Pharmabrust is a co-processed excipient system with specific excipients, which allows rapid disintegration and low adhesion to punches. Pharmabrust is smooth and creamy and helps to mask taste and grittiness of the actives. Main advantages Pharmabrust is highly compatible, rapid disintegration and cost effective [7]. Methocel K4M premium are semi synthetic derivative of cellulose. They are swellable and hydrophilic polymer. They are suitable to use as a retardant material in SR matrix tablets, as they are non toxic and easy to handle [8]. Matrix tablets prepared using Methocel polymer on contact with aqueous fluids gets hydrated to form a

ISSN: 0975-8585

viscous gel layer through which drug will be released by diffusion and/or by erosion of the matrix [9].

MATERIALS AND METHODS

Materials

The Vildagliptin were provided by Popular Pharmaceutical Ltd., Dhaka, Bangladesh. Acetonitrile of HPLC grade was purchased from E. Merck, Darmstadt, Germany. Anhydrous Potassium Dihydrogen Phosphate, Potassium Hydroxide, Phosphoric acid and other reagents were of analytical-reagent grade and purchased from E. Merck, Darmstadt, Germany. Water was deionised and double distilled. Six commercial brands of tablets containing 50 mg Vildagliptin were purchased from local drug shops in Dhaka city after checking their manufacturing license numbers, batch numbers, production and expiry dates.

Preparation of immediate release (IR) sustained release (SR) tablets of Vildagliptin

Immediate release (IR) tablet of Vildagliptin were formulated using superdisintegrating polymer i.e. pharmabrust in increasing amount 10, 20, 30, 40, 60, 70 and 80 mg. In the same way, sustained release (SR) tablet of Vildagliptin were formulated using methocel K4M CR polymer in increasing amount in the same range respectively. The compositions of immediate release tablet FI and sustained release tablet FS are summarized in Table 1 and Table 2.

Table 1: Immediate release formulation of Vildagliptin

Ingredients for Immediate Formulations	FI-1	FI-2	FI-3	FI-4	FI-5	FI-6	FI-7
Vildagliptin	50	50	50	50	50	50	50
Pharmabrust	10	20	30	40	60	70	80
Mannitol	60	60	60	60	60	60	60
Microcrystalline Cellulose (Avicel PH 101)	150	150	150	150	150	150	150
Mg-Stearate	1	1	1	1	1	1	1

Table 2: Sustained release formulation of Vildagliptin

Ingredients for Sustained Formulations	FS-1	FS-2	FS-3	FS-4	FS-5	FS-6	FS-7
Vildagliptin	50	50	50	50	50	50	50
Methocel K4M CR	10	20	30	40	60	70	80
Mannitol	60	60	60	60	60	60	60
Microcrystalline Cellulose (Avicel PH 101)	150	150	150	150	150	150	150
Mg-Stearate	1	1	1	1	1	1	1

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Evaluation of granules

Granules from all the formulation were evaluated for bulk density, compressibily index, angle of Repose.

LBD (Loose Bulk Density) and TBD (Tabbed Bulk Density) were determined by Tab density tester. Initial volume and tapped volume of 2 gm of granules were observed and LBD, TBD, compressibility index and hausner ratio was calculated from the following equations:

LBD = Weight of the powder / volume of the packing.
TBD = Weight of the powder / Tapping volume of the packing.
Carr's index (%) = {(*TBD* – *LBD*) X 100}/*TBD*
Hausner ratio= Tabbed density/ Bulk density

The angle of repose of granules was determined by following granules through the funnel freely to surface. The radius ® and height (h) of the powder cone was measured and angle of repose was calculated using the following equation:

$$\text{Angle of Repose } \vartheta = tan^{-1}\, h/r$$

Where, *h* = Height of the powder cone.
r = Radius of the powder cone

Evaluation of Tablets

All the prepared tablets were evaluated for its uniformity of weight, hardness, friability and thickness according to official methods. The average weights and percentage deviation were calculated by weighing 20 tablets from each brand by an analytical weighing balance. The crushing strength was determined with an Automatic Tablet Hardness Tester (8M, Dr Schleuniger, Switzerland).

HPLC Analysis of Vildagliptin

The HPLC method has been developed by using a mixture of acetonitrile and buffer (30:70 v/v) as a mobile phase which was pumped at a flow rate of 0.5 ml/min through the column (C18; 5µ, 4.6 X 150 mm, Waters, USA) at ambient temperature. The injection volume was 10 µl. The objective is to develop and validate a rapid, selective and sensitive HPLC method for determination of Vildagliptin from its pharmaceutical dosage form that have short and simple extraction procedures, consume small amount of solvent for extraction in a short turnaround time. The method is developed using the protocols set out in the International Conference on Harmonization (ICH) guidelines [10].

20 tablets were accurately weighed and the average weight was calculated. Then one tablet weight 50 mg was taken into 50 ml amber volumetric flask and 3 ml of water is added in it to disperse the tablet, then 30 ml of diluting solution was added and the solution was shake

thoroughly at 250 rpm for 10 minutes by using vortex mixer. Then the volume was adjusted up to the mark with diluting solution. The prepared solution was sonicated for 10 minutes then cooled to room temperature and filtered through whatman filter paper. 1 ml of this solution was taken in 25 ml amber volumetric flask and diluted with diluting solution and volume adjusted up to the mark. Then the resultant solution was filtered through 0.45 µ- disc filter.

Potency determination of Vildagliptin tablets

20 mg equivalent Vildagliptin was taken from each immediate release and sustained release formulation and dissolved in 100 ml water and sonicated. Then again 10 ml was taken from there and volume was adjusted upto100ml. From that solution absorbance was measured. Then the concentarion mcg/ml was calculated. Then the potency was calculated from the obtained result.

Dissolution method development for Vildagliptin tablet

Selection of suitable rpm

The dissolution study of Brand A of Vildagliptin was carried on different paddle rpm (75 and 50) for the selection of suitable rpm.

Selection of dissolution medium

The dissolution study of marketed product of Vildagliptin was carried in different media (Buffer pH 1.2, pH 4.5, pH 6.8, pH 7.8 and water) to select the suitable media for the dissolution study.

***In- vitro* Release Studies of prepared tablets of Vildagliptin**

The *in-vitro* dissolution tests were performed by using the selected rpm, wavelength and dissolution medium. *In-vitro* dissolution study was performed in 900 ml distilled water. The temperature of the medium was maintained at $37^{o}C \pm 0.5^{o}C$ throughout the experiment. The USP dissolution test apparatus type II (Paddle type) was used and the rpm (rotation per minute) was set to 75. At 5, 15, 30, 45 and 60 minutes for immediate release formulations and 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7 and 8 hours for sustained release formulations (10ml) of aliquots were collected for analysis which was then replaced with equal volume of fresh dissolution medium. From the samples collected, absorbance was measured at both λ_{max} values 210 and 212nm using Shimadzu UV – 1700 UV/Visible Double Beam Spectrophotometer (Shimadzu, Japan). Percentage of the drug release was calculated.

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RESULTS AND DISCUSSION

Formulation development of immediate release and sustained release tablets of Vildagliptin

The results of physical parameters (weight, hardness, thickness, LBD, TBD, angle of repose, Compressibility index and disintegration time) and potency of the prepared immediate release tablets are shown in Table 3, 4 and 5. The thickness of the tablets were found between 5.43 ± 0.05 mm to 6.67 ± 0.09 mm, hardness of the tablets ranged from 8.69 ± 0.52 kg/cm^2 to 9.29 ± 0.14 kg/cm^2. And of sustain release tablets are shown in Table 6, 7, 8. The thickness of the SR tablets was found between 4.36 ± 0.04 mm to 4.87 ± 0.12 mm. The weight variations of prepared IR and SR tablets complied with the pharmacopoeial specifications. The drug content of every formulation was found about to 100% of labeled content. So it can be said that physical properties and drug content of the compressed immediate release tablets were satisfactory.

Table 3: Physical properties of the prepared powder of different immediate formulations

Parameters	FI-1	FI-2	FI-3	FI-4	FI-5	FI-6	FI-7
LBD (g/cm^3)	0.3	0.305	0.332	0.332	0.356	0.377	0.385
TBD (g/cm^3)	0.469	0.48	0.498	0.521	0.516	0.58	0.565
Compressibility Index (%)	36.03	36.45	33.33	36.27	31.1	35	31.85
Angle of Repose	50	49	48	52	45	47	49

Table 4: Evaluation of physical properties of IR tablet formulation

Formulation	Average Weight (mg)	Thickness (mm)	Hardness (N)	Disintegration Time (min)
FI-1	261.425	5.43 ± 0.05	8.90 ± 0.60	1.2
FI-2	271.725	5.55 ± 0.1	9.13 ± 0.37	1.3
FI-3	275.225	6.3 ± 0.14	8.82 ± 0.08	1.2
FI-4	278.25	6.48 ± 0.01	8.73 ± 0.24	1
FI-5	292.65	6.55 ± 0.05	9.29 ± 0.14	1.4
FI-6	301.5	6.1 ± 0.08	9.01 ± 0.33	1.2
FI-7	291.5	6.67 ± 0.09	8.69 ± 0.52	1.3

Table 5: Potency determination of immediate release tablet

Formulation Code	Potency %
FI-1	100.60 ± 0.19
FI-2	99.12 ± 0.37
FI-3	99.26 ± 0.42
FI-4	99.67 ± 0.71
FI-5	100.27 ± 0.36
FI-6	99.44 ± 0.21
FI-7	100 ± 0.62

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Table 6: Physical properties of the prepared powder of different sustained formulations

Parameters	FS-1	FS-2	FS-3	FS-4	FS-5	FS-6	FS-7
LBD (g/cm^3)	0.313	0.324	0.353	0.375	0.392	0.412	0.416
TBD (g/cm^3)	0.5	0.506	0.529	0.554	0.562	0.58	0.585
Compressibility Index (%)	37.4	35.96	33.27	32.31	30.24	28.96	28.88
Angle of Repose	48	46	43	42	40	40	38

Table 7: Evaluation of physical properties of SR tablet formulation

Formulation	Average Weight (mg)	Thickness (mm)	Disintegration Time (min)
FS-1	221.65	4.36 ± 0.04	25
FS-2	204.65	4.33 ± 0.01	64
FS-3	238.35	4.39 ± 0.01	120
FS-4	316.85	4.72 ± 0.07	Not disintegrated till 120 min
FS-5	308.55	4.565 ± 0.04	Not disintegrated till 120 min
FI-6	313.75	4.685 ± 0.02	Not disintegrated till 120 min
FI-7	320.8	4.865 ± 0.12	Not disintegrated till 120 min

Table 8: Potency determination of sustained release tablet

Formulation Code	Potency %
FS-1	100.60 ± 0.56
FS-2	99.53 ± 0.37
FS-3	97.80 ± 0.42
FS-4	100.67 ± 0.71
FS-5	98.27 ± 0.47
FS-6	99.00 ±0.89
FS-7	99.39 ±0.19

Dissolution method development

Selection of suitable rpm

The dissolution study of Brand A of Vildagliptin was carried on different paddle rpm for the selection of suitable rpm. The result shows that the percent release of brand A Vildagliptin was greater in the case of 75 rpm as compared to the 50 rpm so we select the 75 rpm for further in vitro dissolution study.

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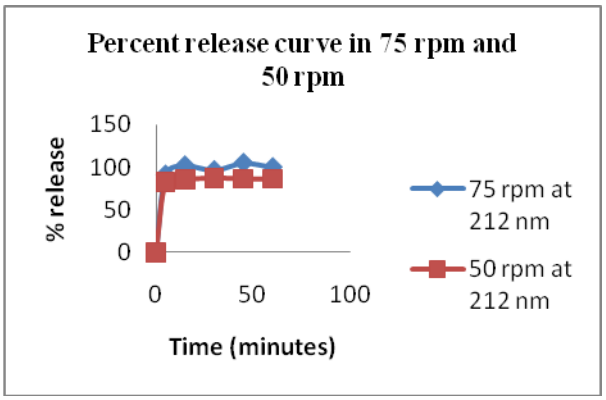

Figure 2: Percent release curve in 75 rpm and 50 rpm

Selection of suitable medium for dissolution study

At first Brand A market product of Vildagliptin was used for dissolution study. In the study different dissolution medium was used, the percent release data of brand A in different dissolution medium is shown in following Figure3 and 4. From the above result we can conclude that the percent release from Brand A product was best in water as a dissolution medium and wavelength at 212nm.

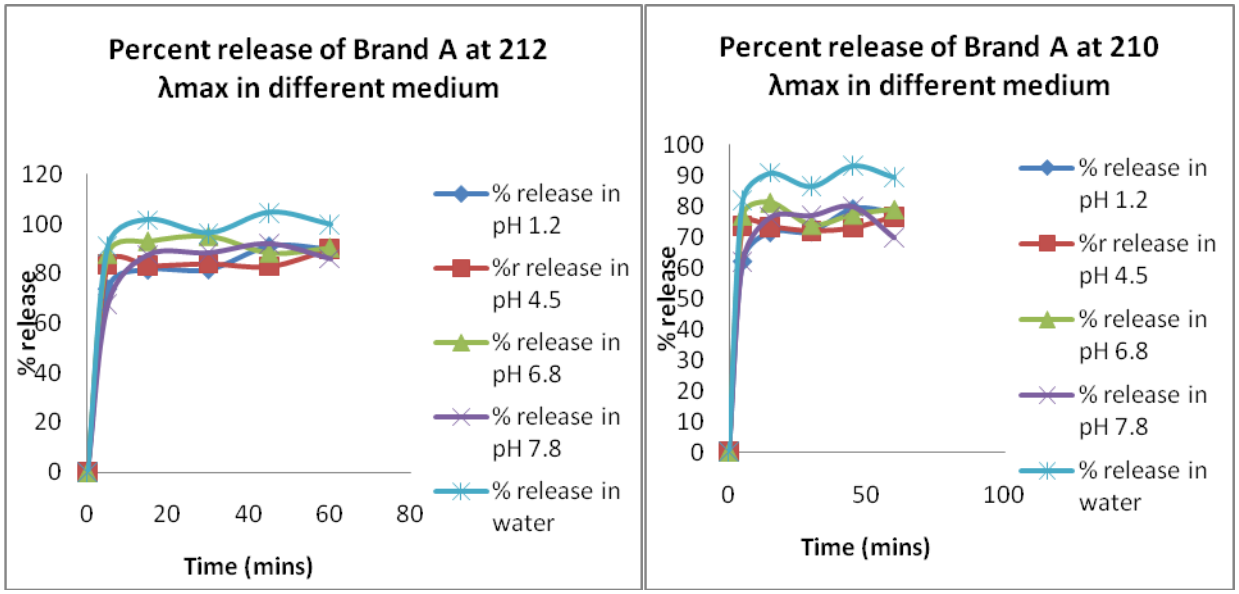

Figure 3: Percent release from Brand A Vildagliptin at 210 nm (left) and 212nm (right)

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HPLC

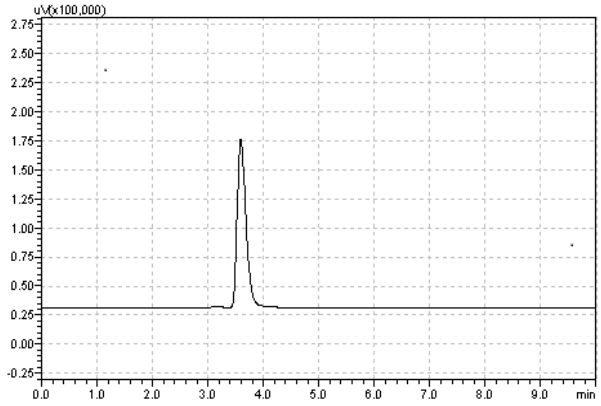

Figure 4: Chromatogram of Vildagliptin

Determination of potency of marketed product of immediate release Vildagliptin tablets by HPLC

The proposed method was used to determine the potency of commercially available tablets (Six brands) containing 50 mg of Vildagliptin. Three replicate determinations i.e. n=3 were carried out and the results are summarized in Figure 5.

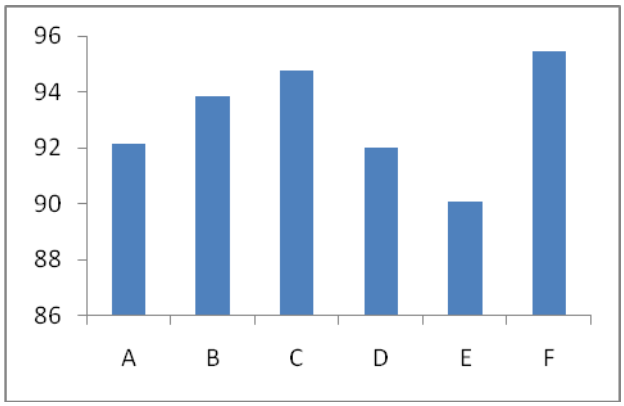

Figure 5: Graph showing potency of marketed product of immediate release tablets of Vildagliptin by HPLC

In the above bar graph, we can see that the market product F has the maximum potency i.e.95.43%. The other products A, B, C, D, E have 92.11%, 93.83%, 94.77%, 91.98% and 90.05% respectively.

In- vitro Release Studies of prepared tablets of Vildagliptin

As from the above market product in vitro dissolution study we are able to select the water as a dissolution medium and value of λmax 212nm. So the *in-vitro* dissolution study of formulated tablet was carried on water medium. The percent release data of seven formulations of immediate release tablet (FI-1 to FI-7) are shown in the following figure 6.

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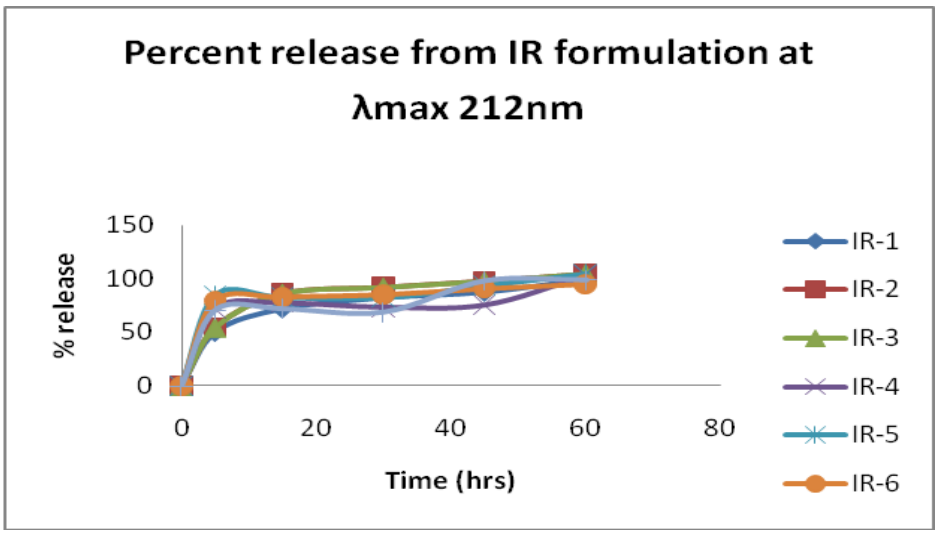

Figure 6: Percent release curve of IR tablets in water at different λmax values

The above result shows that the drug release profile from immediate release tablets was around 100% within an hour for all the formulation. The use of super disintegrating agent in formulation gives the faster release rate [11]. The percent release data of seven formulations of sustained release tablets (FS-1 to FS-7) are shown in the following figure 7. The drug release from the tablet was sustained for 8 hr. Drug release decreased with increase of polymer loading as methocelK4M CR polymers form viscous gelatinous layer (gel layer) upon exposure to aqueous medium by undergoing rapid hydration and chain relaxation and this gel layer acts as the barrier to release of drug and as a result drug release is prolonged.

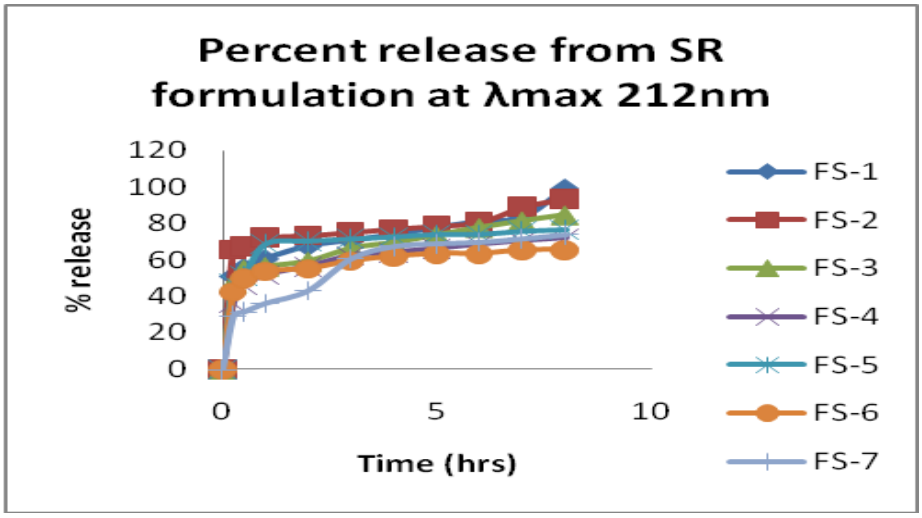

Figure 7: Percent release from SR formulation at λmax 212nm

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Drug release kinetics of sustained release formulations

The correlation coefficients values of the trend lines of the graphs showed that all 7 formulations best fit in First order release pattern, as the highest correlation coefficient i.e. R^2=0.995 was obtained from this drug release kinetics which shows that our sustained release formulations release pattern depends on the initial concentration of drug. As the amount of

drug decreases, the release rate gradually decreases.

Figure 9: First order release curve

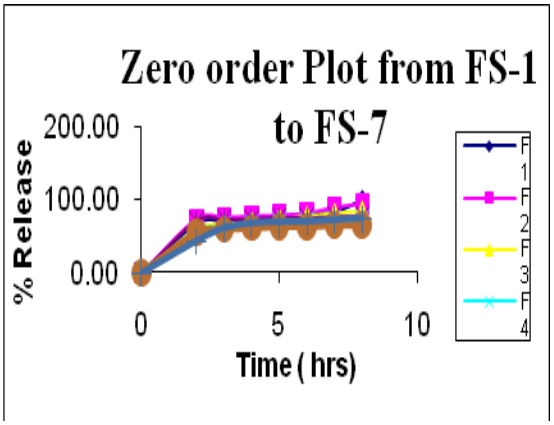
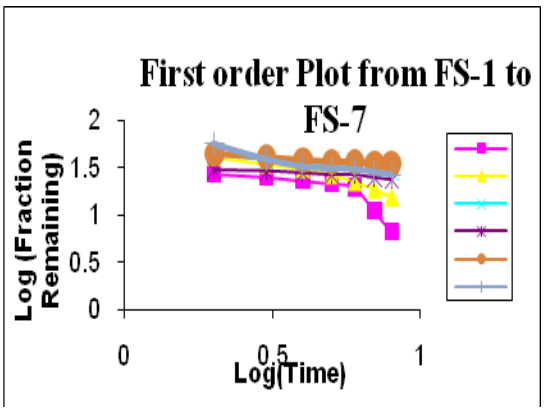
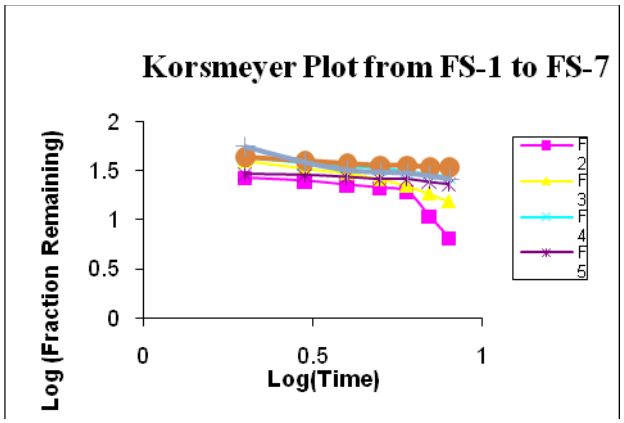


Figure 8: Zero order release curve





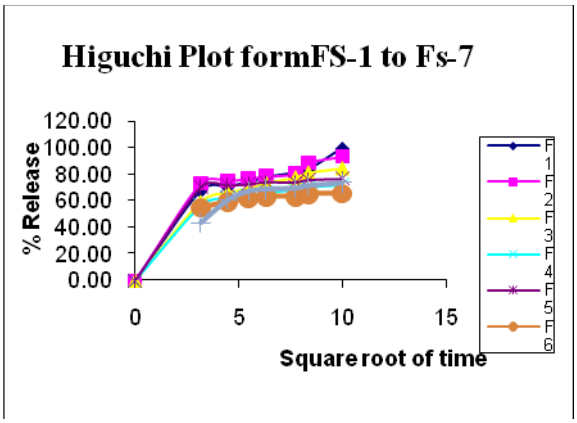


Figure 10: Higuchi curve

Figure 11: Korsmeyer curve

ISSN: 0975-8585

Table 10: Correlation coefficient (R^2) values of different formulation in different plot

	Zero order	1st order	Higuchi	Korsmeyer
	R^2	R^2	R^2	R^2
FS-1	y = 9.504x + 27.66	y = -0.055x + 1.625	y = 31.56x + 8.879	y = 0.751x + 0.059
	R^2 = 0.733	R^2 = 0.983	R^2 = 0.927	R^2 = 0.974
FS-2	y = 8.941x + 31.68	y = -0.093x + 1.706	y = 30.70x + 12.07	y = 0.751x + 0.067
	R^2 = 0.657	R^2 = 0.808	R^2 = 0.888	R^2 = 0.967
Fs-3	y = 8.719x + 25.95	y = -0.068x + 1.748	y = 29.20x + 8.241	y = 0.737x + 0.056
	R^2 = 0.733	R^2 = 0.995	R^2 = 0.943	R^2 = 0.976
FS-4	y = 7.116x + 26.39	y = -0.03x + 1.681	y = 24.78x + 10.12	y = 0.718x + 0.062
	R^2 = 0.639	R^2 = 0.973	R^2 = 0.888	R^2 = 0.970
Fs-5	y = 7.018x +33.57	y = -0.016x + 1.506	y = 25.74x + 15.04	y = 0.731x + 0.076
	R^2 = 0.516	R^2 = 0.972	R^2 = 0.797	R^2 = 0.957
FS-6	y = 6.319x + 26.58	y = -0.017x + 1.664	y = 22.58x + 11.03	y = 0.728x + 0.153
	R^2 = 0.579	R^2 = 0.880	R^2 = 0.848	R^2 = 0.667
FS-7	y = 8.018x + 21.83	y = -0.046x + 1.759	y = 26.72x + 5.803	y = 0.721x + 0.043
	R^2 = 0.736	R^2 = 0.805	R^2 = 0.937	R^2 = 0.983

Table 11: Comparison of dissolution (f1 and f2) data with innovator brand

Immediate release formulations (IR)	f2	f1
FI-1	50.89	14
FI-2	50.98	10
FI-3	50.98	10
FI-4	51.02	13
FI-5	51.38	5
FI-6	51.6	3
FI-7	50.98	13

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Table 11 shows the f1 and f2 values of different brands in respect of innovator brand. Similarity factor f2 has been adopted by FDA (1997) and the European Agency for the Evaluation of Medicinal Products by the Committee for Proprietary Medicinal Products (CPMP) to compare dissolution profile. Two dissolution profiles are considered similar and bioequivalent, if f1 is between 0 and 15 and f2 is between 50 and 100. F-6 seems to be best similar to the innovator brand for higher f2 (51.6) and lower f1 value (3).

Drug-Excipients compatibility studies

Physical compatibility studies were assured by FT-IR studies. The IR spectrums of the mixed powders were taken by preparing potassium bromide pellets under dry condition by using pellet press. Spectra are superimposed. The transmission minima (absorption maxima) in the spectra obtained with the sample corresponded in position and relative size to those in the spectrum obtained with the working/reference standards. The polymer and the drug compatibility were evaluated by spectral as show in Figure 12, 13 and 14.

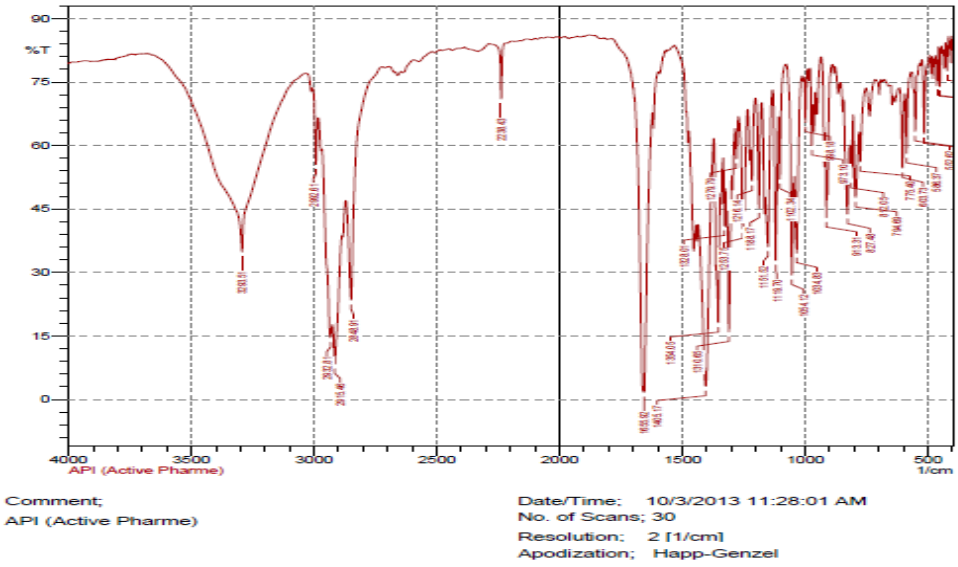

Figure 12: FT-IR Spectra of pure drug Vildagliptin

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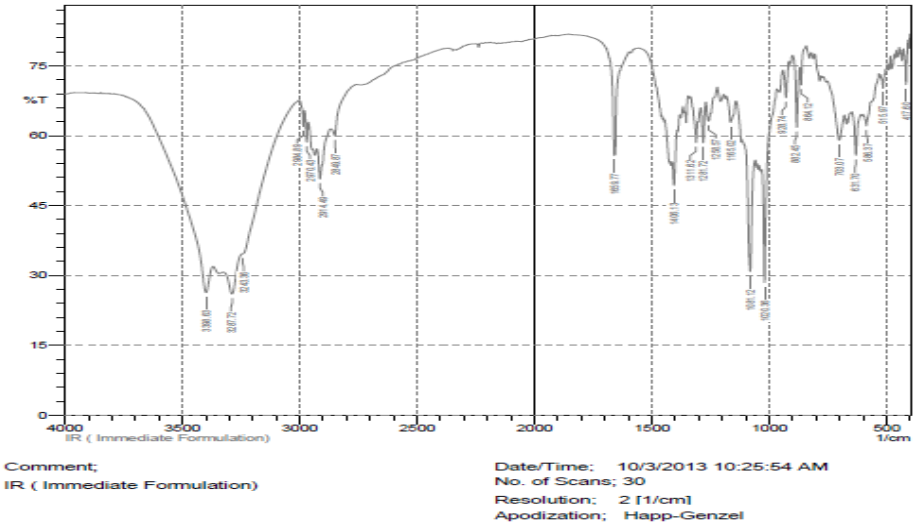

Figure 13: FTIR Spectra of immediate release formulation of Vildagliptin

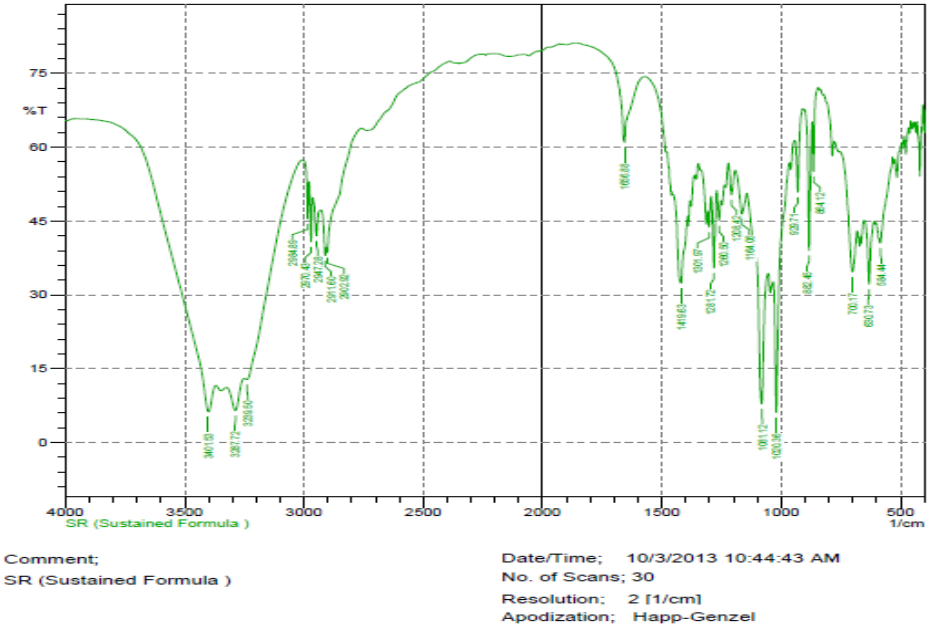

Figure 14: FTIR Spectra of sustained release formulation of Vildagliptin

CONCLUSION

The present work was to design the immediate and sustained release tablets of Vildagliptin and their in-vitro study. The immediate release tablets were prepared by using pharmabrust as superdisintegrating agent. The use of super disintegrating agent in formulation gave the faster release rate. The sustained release tablets were prepared by using methocel K4M CR as retardant polymer. Drug release decreased with increase of polymer loading as

methocelK4M CR polymer form viscous gelatinous layer which acts as the barrier to release of drug and as a result drug release is prolonged.

ACKNOWLEDGEMENT

The authors are thankful to the management and lab technicians of University of Asia Pacific, Department of Pharmacy, Dhaka, Bangladesh for providing the necessary facilities to carry out this work.

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