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PREPARATION AND EVALUATION OF SUSTAINED RELEASE PELLETS OF SAXAGLIPTIN BY EXTRUSION-SPHERONIZATION

Balasaheb B. Nishane*[1], Kailas N.Tarkase[1], Madhurani K. Tarkase[2] and Mahesh D. Dokhe[1]

[1]Department of Quality Assurance Technique, DR.V.V.P.F's College of Pharmacy (SavitribaiPhule Pune University), Vilad Ghat, Ahmednagar-414111, Maharashtra, India.

[2]Department of Pharmaceutical Chemistry, DR.V.V.P.F's College of Pharmacy (SavitribaiPhule Pune University), Vilad Ghat, Ahmednagar-414111, Maharashtra, India.

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***Corresponding Author**
Balasaheb B. Nishane
Department of Quality Assurance Technique, DR.V.V.P.F's College of Pharmacy (SavitribaiPhule Pune University), Vilad Ghat, Ahmednagar-414111, Maharashtra, India.

ABSTRACT

The present search engrossed on the preparation and evaluation of sustained released pellets of Saxagliptin using a different grade of polymers like Eudragit L and Eudragit RLPO as a sustained released polymer. Pellets were prepared by using Extrusion spheronization method in which water was used as a solvent and microcrystalline cellulose which acts as the spheronization aid. The pellets were prepared and evaluated for the pre-formulation studies like Bulk density, Tapped density, Compressibility index, and Hausner"s ratio. Evaluation parameters were found within a standard range which indicated that pellets were prepared by Extrusion-spheronization processes having a satisfactory result for further studies. Friability of pellets was found to be within standard range.DSC and FT-IR studies confirmed the compatibility of the drug with the polymer in the drug-loaded polymer. The prepared formulation was spherical in nature confirmed by SEM photography and sphericity factor. Drug content was in the range of 99.25%. Stability studies were carried out for a period of 90 days 40 ^{0}c 75 RH hence pellets was found to be stable in nature.

KEYWORDS: Saxagliptin, Eudragit L, Eudragit RLPO, microcrystalline cellulose, Extrusion-spheronization method, In-Vitro study.

INTRODUCTION

The purposed of manufacturing sustained released system is to reduce the dosing frequency or to increase the effectiveness of the drug by a local route at the site of action, reduced the dose required for uniform drug delivery[1] attaining the therapeutics blood level for the longer period of time for that it follow the zero order kinetics. Zero-order kinetics is the independent of the amount of concentration of drug released in the drug delivery system. The current scenario based on the formation of the multiple unit pellets where a coating of the drug with sugar sphere and further coatings gives the sealing of the drug and to obtain sustain release dosage form, by the process palletization method. Palletization method in which size widening processes are carried out and the formed product obtained is called pellets. The word 'pellet' has been used to define a variety of method used to produce, geometrically defined agglomerates attained from varied starting materials employing different processing conditions. Oral dosage form which consisting of the small unit each having the specific characteristic.[2-3] Pellets provide a decrease in the dosage regimen and additionally controlling the drug release and increasing the absorption of the active ingredient. Pellet having the advantage is that it is the good candidate for the delivery of drug substances because the pellets reduced the dumping effect of the drug. The reproducibility of the release characteristics from pellet preparations is also much better with respect to the single-unit dosage forms. They produced resistance to the external factors such as moisture, air and light are the most advantageous properties of this dosage forms.[4-5] The present research was mainly concentrated on the formulation and evaluation of sustained release pellets of saxagliptin with different grades of Eudragits by applying extraction spheronization method. Different grades of Eudragits were used in the present work and Eudragit L and Eudragits RLPO the combination of the both was found to have a satisfactory drug release.

MATERIAL AND METHODS

Material

Saxagliptin was obtained as a gift sample from Glenmark, Pharmaceutical Ltd. (Mumbai, India), Eudragit L, Eudragit RLPO from Evonik Pharma Ltd. (I), All other chemicals and reagents used were of AR grade.

METHOD

Saxagliptin sustained release pellets were prepared by an Extrusion-spheronization method by using Eudragit L and Eudragit RLPO as sustained release polymer.[6]

UV-Visible Spectroscopic Scanning

Determination of UV Spectrum in Phosphate Buffer pH 6.8.

The stock solution of Saxagliptin (100µg/ml) was prepared by dissolving it in phosphate buffer pH 6.8. A dilution of 15 µg/ml was kept in a cuvette of path length 10 mm. The UV spectrum was recorded using double beam UV-VIS spectrophotometer in the wavelength range 200 nm – 400 nm.[12-13]

Calibration curve of the drug

Preparation of Standard Curve in Phosphate Buffer pH 6.8.

A stock solution of Saxagliptin(100 µg/ml) was prepared by dissolving 10 mg of drug in phosphate buffer pH 6.8 and final volume was made to 100 ml. The solutions in the concentration range of 2-12 µg/ml were prepared by appropriate dilutions of stock solution. The UV absorbance of these solutions was determined spectrophotometrically at λ max 210 NM.[13]

Formulation of Pellets

Drug-Loaded Pellets were prepared by weighing the required quantity of Saxagliptin, microcrystalline cellulose, Eudragit L, Eudragit RLPO in distilled water. The wet mass was immediately passed through an extruder with 1mm sieve. Extrudate so obtained were spheronized in Spheronizer having cross line plate of size 4.2 mm.[6,10-11]

Table 1: Formula as per experimental plan for Sustained release polymer.

Ingredients	B1	B2	B3	B4	B5	B6	B7	B8	B9
Saxagliptin	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Eudragit L	4	4	4	6	6	6	8	8	8
Eudragit RLPO	8	12	16	8	12	16	8	12	16
MCC	85.5	81.5	77.5	83.5	79.5	75.5	81.5	77.5	73.5
Distilled Water	qs.	qs.	qs.	qs.	qs.	qs.	qs.	qs.	qs.

All values are in %

Evaluation of Pellets

The pellets evaluated for in-process quality control test-[14-15]

Flow properties of pellets

Determination of Bulk Density and Tapped Density

An accurately weighed quantity of the granules/powder (W) was carefully poured into the graduated cylinder and volume (V0) measured. Then the graduated cylinder was closed with a lid and set into the tap density tester (USP). The density apparatus set for 100 tabs and after that, the volume (Vf) measured and continued operation till the two consecutive readings were equal. The bulk density and the tapped density calculated by using below formulae-

Bulk density = W/V0

Tapped density = W/Vf

Where, W= Weight of the powderV0 = Initial volumeVf = final volume

Compressibility Index (Carr's Index)-

Carr's index (CI) is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flow able it is.

CI = (TD-BD) x 100/TD

Hausner's Ratio

It is the ratio of tapped density and bulk density. Generally, a value less than 1.25 indicates good flow properties, which is equivalent to 20% of Carr's index.

Friability

Accurately weighed the quantity of pellets (3 gm) taken from a final batch of pellets and placed in friabilator and tumbled for 100 revolutions at 25 rpm. After friability testing, the pellets were sieved by using sieve no. 20. The weight loss (%) was calculated by below formulas:[15]

% F = (Wi-Wr/Wi) 100

Wi is initial weight of pellets before friability testing,

Wr is the weight of pellets retained after friability testing

Drug Content

Accurately weighed 28 mg of pellets (equivalent to 10 mg. of drug) were crushed in a dried mortar pestle. Powder of pellets was dissolved in 100 ml with phosphate buffer pH 6.8. The sample was stirred for 15 min and filtered. Dilutions of solution were prepared and Analyzed by UV-spectrophotometer at 210 NM.[16]

Morphological Characteristic of All Batches

All the factorial batches were studied for morphological features like roundness, Aspect Ratio.

Scanning Electron Microscope

Scanning electron microscopy (SEM) is the technique of choice for measuring the shape and surface morphology of pellets.

Drug Excipients Interaction Study

Fourier Transform Infrared Spectroscopy (FT-IR)

It was determined by FT-IR (PRESTIGE-21, Shimadzu). The baseline correction was done with blank background measurement. Then the spectrum of the dried drug was run. FT-IR spectra were recorded in the wavelength region of 4000 to 500 cm $^{-1}$.[14,15]

Differential Scanning Calorimetry (DSC)

The 3.41 mg of sample was weighed and sealed in an aluminum pan. Empty aluminum pan was used as a reference. DSC thermogram was recorded.

In-Vitro Drug Release Studies

The in vitro release of the drug from pellets of all prepared batches were performed by using USP apparatus Type I (Basket). The dissolution medium consisted of 900 ml of phosphate buffer pH 6.8. Dissolution was performed at 37±0.5°C, with stirring speed of 50 rpm. 5 ml of the aliquot was withdrawn at time intervals of 1, 2, 4, 6, 8, 10, 12 Hrs. The medium was replenished with the same amount of fresh dissolution media each time. The filtered samples were analyzed by UV-VIS spectrophotometer at 210 nm and absorbance was record.[14]

Kinetics of Drug Release

The dissolution profile of all the preparations was fitted to, first-order zero order kinetics, Korsmeyer-Peppas Higuchi, Hixson-Crowell to ascertain the kinetic modeling of drug release by using a PCP Disso Version 2.08 software, and the model with the higher correlation coefficient was considered to be the best model.[16]

RESULT AND DISCUSSION

UV-Visible Spectroscopic Scanning- Spectral Analysis

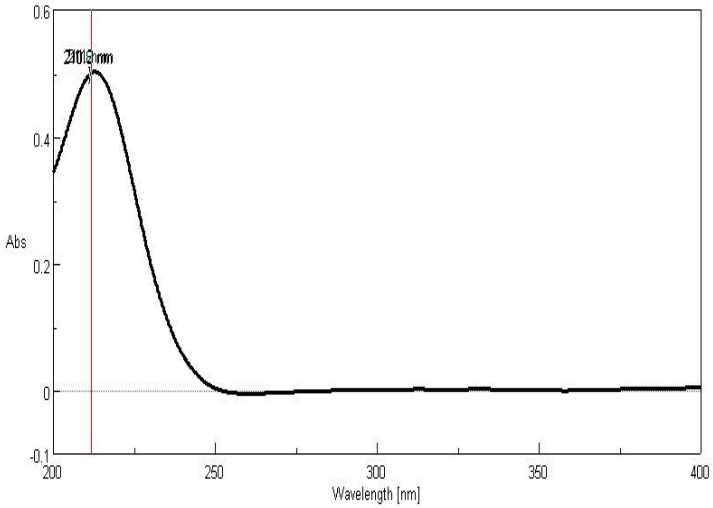

Figure 1: Wavelength maxima of Saxagliptin phosphate buffer pH 6.8 (Conc. 15 ppm) 210 nm.

Table 2: Standard calibration curve data for Saxagliptin in phosphate buffer pH 6.8.

Sr. No.	Concentration (µg/ml)	Absorbance at 210 nm. ± SD.
1.	2	0.2014 ± 0.003
2.	4	0.4024 ± 0.001
3.	6	0.6100 ± 0.002
4.	8	0.8067± 0.004
5.	10	1.0250 ± 0.003
6	12	1.9701± 0.002

* Each value was an average of three determinations

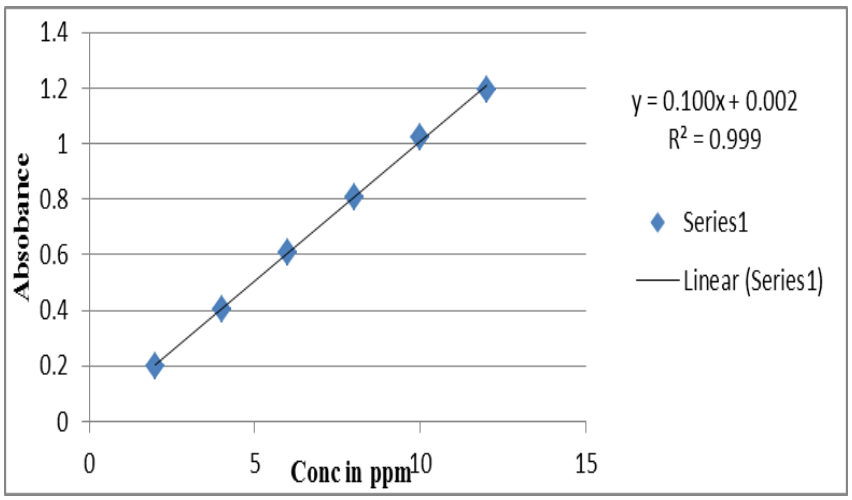

Figure 2: Calibration curve of Saxagliptin phosphate buffer pH 6.8 (Linearity saxagliptin).

Drug-Polymer Interaction Study

FT-IR

The drug was found compatible with the polymer.

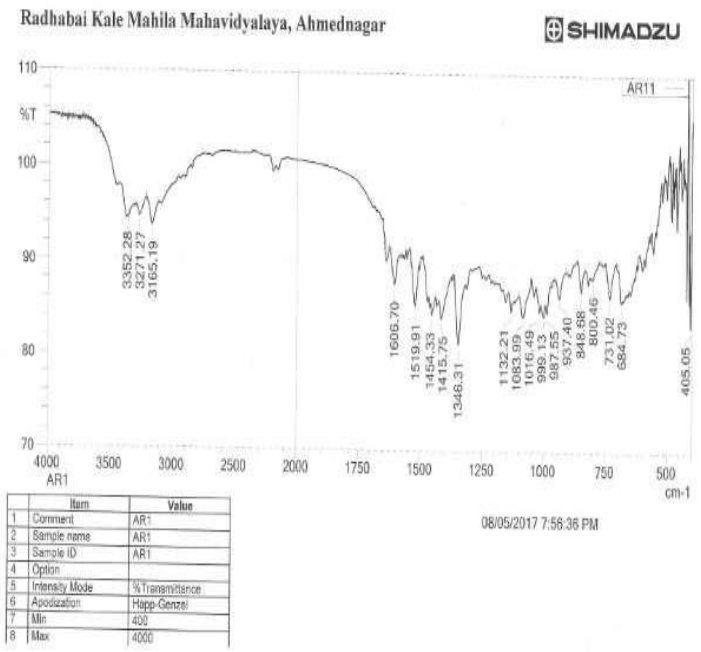

Figure 3: FTIR Spectra of API Saxagliptin.

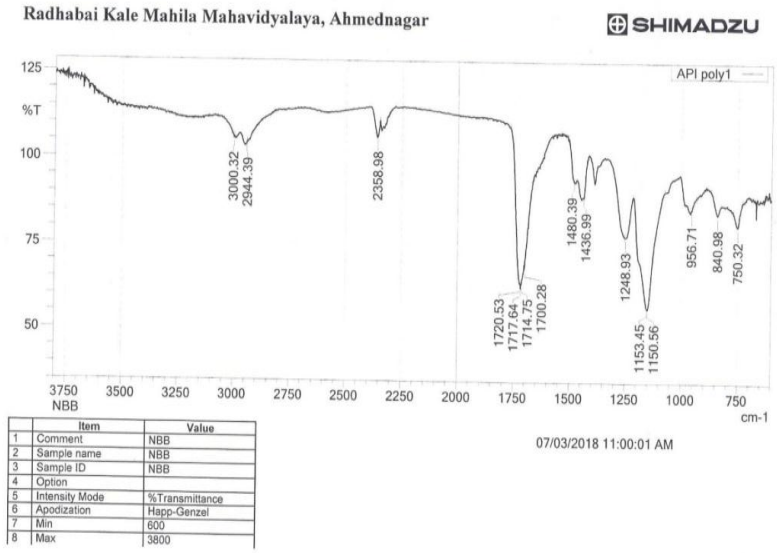

Figure 4: FTIR Spectra of API Saxagliptin with excipients.

Differential Scanning Colorimetry (DSC)

The Thermogram of Saxagliptin showed an endothermic peak at 214.7 ^{0}C. With an onset at 210.3^{0}C.

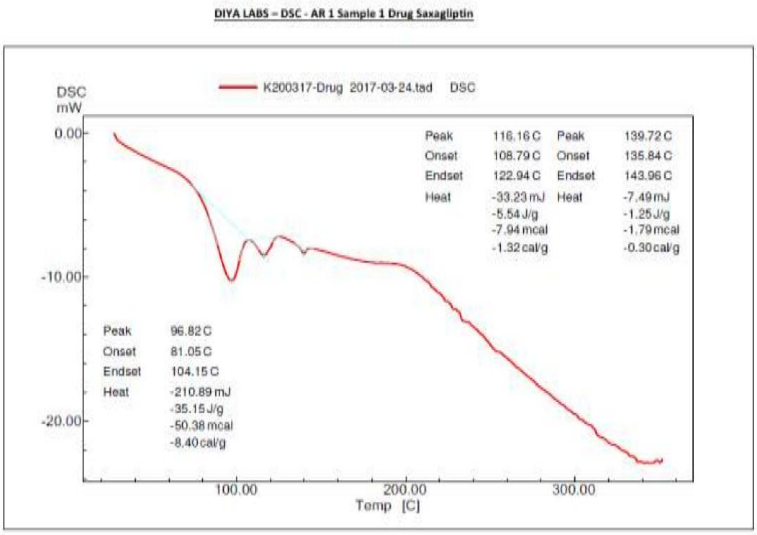

Figure 5: DSC thermogram saxagliptin.

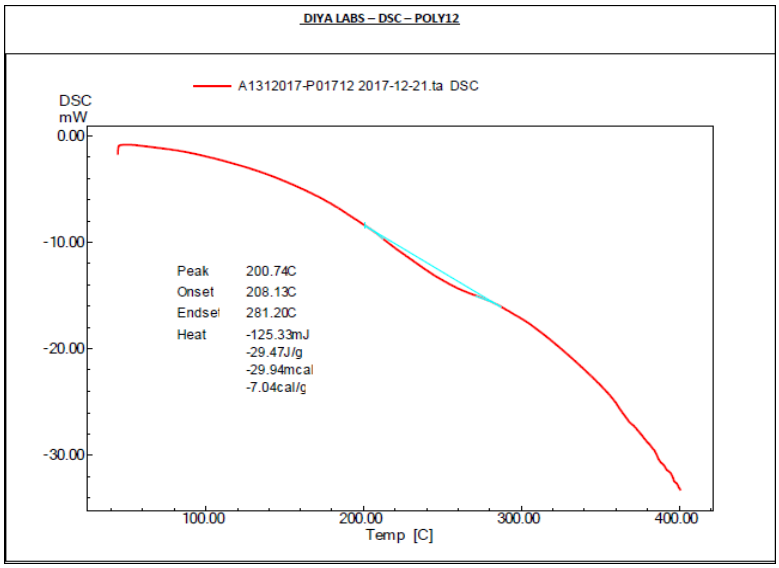

Figure 6: DSC thermogram of Saxagliptin with an excipient.

Evaluation of Flow Properties of Pellets

The flow properties of pellets were a most important parameter for filling pellets into the capsule shell. The value of angle of repose, Carr's index and Hausner's ratio shows excellent flow properties of pellets. All the factorial batches were evaluated for flow property.

Table 3: Evaluation Parameter of Pellets.

Flow property	the angle of repose(Θ)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's index (%)	Hausner's ratio
B1	23.12±0.40	0.76±0.002	0.83±0.005	8.40±0.21	1.09±0.001
B2	24.01±0.25	0.78±0.003	0.85±0.004	8.23±0.23	1.08±0.002
B3	23.02±0.61	0.80±0.004	0.88±0.003	9.09±0.56	1.1±0.004
B4	24.02±0.50	0.79±0.005	0.86±0.007	8.13±0.39	1.08±0.003
B5	23.22±0.55	0.80±0.002	0.86±0.009	6.97±0.65	1.07±0.002
B6	24.20±0.25	0.75±0.004	0.82±0.008	8.53±0.45	1.09±0.001
B7	24.02±0.12	0.73±0.005	0.80±0.003	8.75±0.41	1.09±0.002
B8	23.25±0.45	0.70±0.004	0.77±0.005	9.09±0.32	1.1±0.001
B9	24.28±0.56	0.77±0.002	0.83±0.008	7.22±0.25	1.07±0.003

Morphological Characteristics of All Batches

Aspect ratio nearer to 1 which shows roundness nearer to 100% shows spherical pellets.

Table 4: Morphological Characteristics of Pellets.

Batches	Shape	Aspect ratio	Roundness
B1	Sphere	1.088	41.667 - 48.077
B2	Sphere	1.095	87.128-93.248
B3	Sphere	1.086	87.128 - 93.125
B4	Sphere	1.075	59.753 - 78.351
B5	Sphere	1.086	91.85-99.106
B6	Oval + Sphere	1.112	64.741- 99.045
B7	Sphere	1.08	89.85- 93.989
B8	Oval + Sphere	1.16	46.194-56.511
B9	Dumbbell +Ellipsoid	1.19	60.456 - 78.735

Friability

The friability of the pellets tested was below 0.1%, thus the pellets have desirable hardness and of good quality with respect to friability. The preliminary aim to maintain mechanically strong pellets was there by achieved.

Drug Content

The drug-loaded pellets of Saxagliptin prepared. Drug content of all batches is as shown in Table. All values expressed as mean.

Table 5: Friability and Content Uniformity (%).

BATCH	B1	B2	B3	B4	B5	B6	B7	B8	B9
Friability (%)	0.12±0.02	0.13±0.03	0.13±0.05	0.15±0.05	0.16±0.03	0.15±0.03	0.15±0.01	0.14±0.08	0.16±0.08
Drug content	96.25±0.57	95.23.62±0.23	96.19±0.27	97.25±1.06	98.35±1.02	99.25±0.32	95.25±0.23	97.32±1.05	98.09±0.25

Scanning Electron Microscopy (SEM)

The surface of pellets as shown in SEM photograph was smooth and spherocity was also good and size of pellets was found to be 965 µm to 1011.21 µm and the ratio of length to width (Aspect ratio) is 1.112 which indicates pellets are spherical in shape.

Figure 7: SEM analysis of B6 batch.

In-Vitro Drug Release Studies

These drug release controlled due to Eudragit L &Eudragit RLPO as it is hydrophobic. In-vitro drug release study of all formulation batches (B1to B9) was performed in triplicate using USP apparatus Type-I (Basket).

Time	B1	B2	B3	B4	B5	B6	B7	B8	B9
1	6.051± 0.12	6.755±0. 29	6.640± 0.50	6.925±0. 68	7.100± 0.23	**6.675±0. 23**	5.125±0. 1.07	5.350± 0.54	6.308±0. 20
2	12.910 ±1.25	13.229± 1.06	12.195 ±0.58	11.972±1 .05	12.553 ±0.48	**12.691± 0.31**	14.230± 0.85	10.470 ±0.57	15.903±0 .40
3	19.125 ±0.88	18.763± 0.56	18.460 ±0.25	17.097±0 .54	18.197 ±0.55	**19.846± 0.25**	18.620± 0.26	19.485 ±0.16	25.107±0 .55
4	20.930 ±0.59	24.389± 0.37	26.104 ±0.21	25.948±0 .59	29.444 ±0.66	**27.725± 0.31**	23.656± 0.25	25.560 ±0.45	29.454±0 .68
5	28.655 ±0.12	31.177± 0.78	35.908 ±0.57	33.754±0 .65	39.868 ±0.82	**35.639± 0.40**	33.456± 0.25	38.920 ±0.73	47.238±0 .85
6	50.493 ±1.14	46.858± 0.551	35.908 ±0.57	33.754±0 .65	39.868 ±0.82	**53.649± 0.45**	50.347± 1.05	57.263 ±0.16	70.709±0 .86
7	61.654 ±0.16	51.748± 0.415	61.523 ±1.11	61.190±0 .14	57.230 ±0.51	**60.673± 0.49**	57.300± 1.19	65.451 ±0.71	78.310±0 .50
8	69.181 ±0.19	60.627± 0.25	70.899 ±1.02	69.966±0 .70	65.123 ±0.60	**70.472± 0.36**	72.250± 0.80	79.624 ±0.72	81.153±0 .68
9	78.276 ±0.76	73.159± 0.274	74.200 ±0.59	75.197±0 .39	76.098 ±0.67	**75.248± 0.44**	78.859± 0.45	87.562 ±0.19	90.769±0 .61
10	84.149 ±0.49	88.807± 0.454	84.852 ±1.02	86.600±0 .71	87.557 ±0.81	**86.118± 0.48**	84.373± 0.73	94.172 ±0.10	93.527±0 .88

11	90.501 ±0.47	95.869± 0.39	88.034 ±0.85	89.875±0 .90	90.486 ±0.15	**89.602± 0.32**	95.145± 0.50	96.047 ±0.73	95.746±0 .11
12			96.799 ±0.25	97.200±0 .74	98.250 ±0.45	**99.250± 0.30**	98.450± 0.36	98.501 ±0.13	97.998±0 .42

% Cumulative drug release from batch (B1-B9)

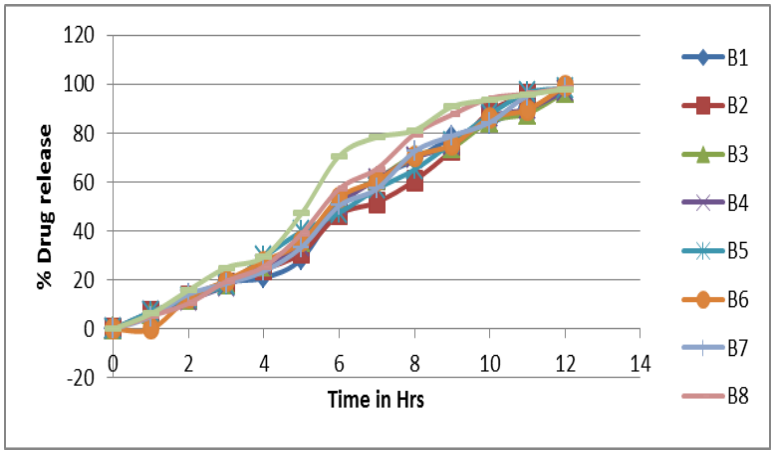

Figure 8: In-vitro % Drug release of all Factorial batches.

Kinetics of Drug Release

In-Vitro Release Kinetics and Mechanism

The pellets, release data was evaluated by model-dependent (curve fitting) method using PCP Disso-v3 software and model with the higher correlation coefficient was considered to be the best model. To know the release mechanism and kinetics of formulations (B6) were attempted to fit into mathematical models. $R^2$was taken as criteria for selecting the most appropriate model. The Korsmeyer-Peppas kinetic model was best fit for formulation (B6) (R^2= 0. 0.9990); represented in Table 6.

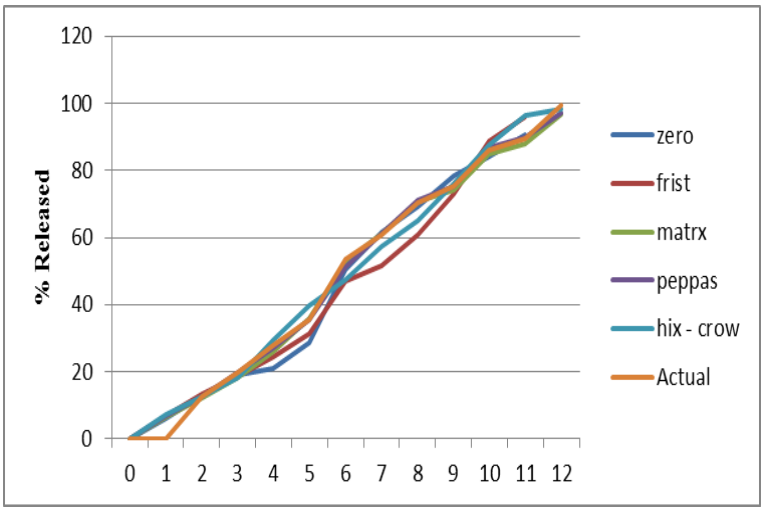

Figure 9: In-vitro Release Kinetic.

Table 6: Drug Release Kinetics.

Zero-order	1st Order	Matrix	Korsmeyer-Peppas	Hix. Crow
0.4050	0.9560	0.9365	**0.9990**	0.9045
			Best Fit Model	

Stability Studies

He selected formulations were packed in their final (amber colored glass) containers and are tightly closed with the cap. They were stored at the stated conditions for three months. Samples were analyzed after 0, 30, 60 and 90 days 40 ^{0}c 75 RH and they were evaluated.

Table 7: Stability studies.

Parameter		1 month	2month	3month
Change in appearance	Colour	No changes	No changes	No changes
	clearity	No changes	No changes	No changes
	Surface texture	No changes	No changes	No changes
Drug content (%)		99.25±0.02	99.25±0.02	99.25±0.01

CONCLUSION

The objective of this study was to prepared and evaluate Saxagliptin loaded pellets by the process of extrusion/spheronization mechanisms for the sustained release drug delivery system. It was observed that Eudragit L enhanced the release of Saxagliptin from drug loaded pellets whereas Eudragit RLPO retarded the same. In order to obtain a sustained released drug delivery, a combination of these polymers in different concentration was tried and found to be the satisfactory result and which encenced the released of the drug in the sustained drug delivery system. It was concluded that a combination of Eudragit L and Eudragit RLPO in 6% w/v and 16% w/v respectively showed sustained release (99.25 % in 12 hr) effect. This developed combination for the sustained released system which contributes the most important role in the novel drug delivery system.

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REFERENCE

1. Dr. DheerajT.Bhviskar,Dr. Dinesh K. Jain, "Noval drug Delivery System", 1st edition-july "Nirali prakshan", 2012; 2.1-2.3
2. Davis SS, Hardy JG, Fara JW. Transit of pharmaceutical dosage forms by the small intestine. Gut, 1986; 27: 886-892.
3. Dashevsky A, Kolter K, "Independent Ph release of a basic drug from pellets coated with the sustained release polymer dispersion", 2004; 58: 45-49.
4. Wu XY, Eshun G, Zhou Y. "Effect of interparticulate interaction on the kinetics releaseof microspheres ensembles" J Pharm Sci, 1999; 87: 586-593.
5. ZHon Y, Wu XY." Modeling and evaluation of dispersed drug release into a finite medium from sphere ensembles with a boundary layer": 90: 23-36.
6. Vervaet and Lakshmi, PK, "Extrusion-Spheronization-A Review", International Journal of Pharm tech Research, 2010; 2429-2433.
7. Sweetman, CS, "Martindale, the Complete Drug Reference", 33rd Ed., Pharmaceutical Press, London, 2010; 315-316,322-332, 334-335.
8. M, Srujan Kumar at al, "Formulation and Evaluation of Venlafaxine Hydrochloride of Multiunit Pellet System", Journal of Pharmaceutical and Biomedical Sciences, 2012; 18(1): 1-12.
9. DM, Mathure et al, "Formulation and optimization of cetrizinedihydrochloride controlled release pellets", 2011; 3(3): 443-452.
10. Pavia, Lampmanand Kriz, X Vyan, "Spectroscopy", Indian Edition, 2007114-101.
11. GR, Chatwaland SK, Anand, "Instrumental Method of Chemical Analysis", Himalaya Publishing House, 9.15-9.40. 15. US, Pharmacopoeia (USP/NF)(2008), "The Official Compendia of Standards'', Asian Edition, 2012; I 813.
12. Lachman, L; Lieberman, et-al, "The Practice of Industrial Pharmacy Theory and", 2nd Edition. Varghese Publishing House, Mumbai, 293. 3. Chein, YW, "Novel Drug Delivery Systems", 2nd Ed., 1992 Vol.-II, Marcel Dekker Inc, New York, 2695.
13. "Indian Pharmacopoeia", Indian Pharmacopoeial Commission, Ministery of Health and Science Welfare, Government of India, Ghaziabad, 2007; 678-679
14. Bramankar, DM and Jaiswal, S B, "Biopharmaceutics and Pharmacokinetics A Treatise", 1 Ed., Vallabhprakashan, Delhi, 1995; 335,337.
15. KD, Tripthi, "Essential of Medical Pharmacology", 6th Edition, Jaypee Brothers, 2010; 136-141.

16. ICH Guidelines Q1A (R2), "Guidance for Industry: Stability Testing of New Drug Substance and Products", Http:// Http://Www.Ich.Org.
17. Iyer RM, Augsburger LL, Parikh DM. Evaluation of drug layering:Effect of processes binder level. Drug DevInd Pharm, 1993; 19: 981-998.
18. www.drugbank.com/saxagliptin.