NANOPARTICLE FORMULATION OF SITAGLIPTIN PHOSPHATE - A NOVEL THERAPEUTIC OPTION FORDIABETES MELLITUS

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Abstract: The present study was to formulate sitagliptin phosphate nanoparticles by using enteric coated polymers so that the drug is to be released in the small intestine for absorption , bypass the stomach, therefore to reduce side effects which results in improved better patient compliance. The results of FT-IR study showed that there is no interaction between the drug and the polymers. The sitagliptin phosphate nanoparticles were prepared by Double Emulsion Solvent Evaporation (DESE) method. The percentage yields, encapsulation efficiency and drug loading of all formulations were calculated. *Invitro* study showed that burst release of the drug was occurred in acid buffer followed by sustained release of drug for 12 hrs. The burst effect of the best formulations were decreased due to the polymer concentration compared to the other formulations. The best formulations were selected based on the encapsulation efficiency and *invitro* drug release study. F6 and F12 were showed the high encapsulation efficiency compared to the other formulations but drug loading was decreased due to the increase in the polymer concentration. The particle size, zeta potential, polydispersity index for the best formulations were evaluated. Zeta potential indicated that the nanoparticles have good stability. Polydispersity index showed that the nanoparticles size distribution have high homogenicity. The best formulations were fitted into Zero Order kinetic model and it followed Non Fickian Diffusion kinetics. Hence it was concluded that the sitagliptin nanoparticles were prepared successfully by the DESE method. From the results, it was observed that the drug polymer concentration influences the encapsulation efficiency and *invitro* drug releasestudy. The nanoparticles showed that the burst release of drug on acid buffer itself andfollowed by the sustained release of the drug for 12hrs. Therefore, it could be a novel therapeutic option for the treatment of type II diabetes mellitus.

Keywords: Nanoparticle, Formulation, Sitagliptin Phosphate, A Novel Therapeutic Option, Diabetes Mellitus

INTRODUCTION:

Since ancient times, humans have widely used plant-based natural products as medicines against various diseases. Modern medicines are mainly derived from herbs on the basis of traditional knowledge and practices. Nearly, 25% of the major pharmaceutical compounds and their derivatives available today are obtained from natural resources [1, 2]. Natural compounds with different molecular backgrounds present a basis for the discovery of novel drugs. A recent trend in the natural product-based drug discovery has been the interest in designing synthetically amenable lead molecules, which mimic their counterpart's chemistry [3]. Natural products exhibit remarkable characteristics such as extraordinary chemical diversity, chemical and biological properties with macromolecular specificity and less toxicity. These make them favorable leads in the discovery of novel drugs [4]. Further, computational studies have helped envisage molecular interactions of drugs and develop next-generation drug inventions such as target-based drug discovery and drug delivery.

Despite several advantages, pharmaceutical companies are hesitant to invest more in natural product-based drug discovery and drug delivery systems [5] and instead explore the available chemical compounds libraries to discover novel drugs. However, natural compounds are now being screened for treating several major diseases, including cancer, diabetes, cardiovascular, inflammatory, and microbial diseases. This is mainly because natural drugs possess unique advantages, such as lower toxicity and side effects, low-price, and good therapeutic potential. However, concerns associated with the biocompatibility, and toxicity of natural compounds presents a greater challenge of using them as medicine. Consequently, many natural compounds are not clearing the clinical trial phases because of these problems

[6,7,8]. The use of large sized materials in drug delivery poses major challenges, including in vivo instability, poor bioavailability, and poor solubility, poor absorption in the body, issues with target-specific delivery, and tonic effectiveness, and probable adverse effects of drugs. Therefore, using new drug delivery systems for targeting drugs to specific body parts could be an option that might solve these critical issues [9, 10]. Hence, nanotechnology plays a significant role in advanced medicine/drug formulations, targeting arena and their controlled drug release and delivery with immense success.

Nanotechnology is shown to bridge the barrier of biological and physical sciences by applying nanostructures and nanophases at various fields of science [11]; specially in nanomedicine and nano based drug delivery systems, where such particles are of major interest [12, 13]. Nanomaterials can be well-defined as a material with sizes ranged between 1 and 100 nm, which influences the frontiers of nanomedicine starting from biosensors, microfluidics, drug delivery, and microarray tests to tissue engineering [14,15,16]. Nanotechnology employs curative agents at the nanoscale level to develop nanomedicines. The field of biomedicine comprising nanobiotechnology, drug delivery, biosensors, and tissue engineering has been powered by nanoparticles [17]. As nanoparticles comprise materials designed at the atomic or molecular level, they are usually small sized nanospheres [18]. Hence, they can move more freely in the human body as compared to bigger materials. Nanoscale sized particles exhibit unique structural, chemical, mechanical, magnetic, electrical, and biological properties. Nanomedicines have become well appreciated in recent times due to the fact that nanostructures could be utilized as delivery agents by encapsulating drugs or attaching therapeutic drugs and deliver them to target tissues more precisely with a controlled release [10, 19]. Nanomedicine, is an emerging field implementing the use of knowledge and techniques of nanoscience in medical biology and disease prevention and remediation. It implicates the utilization of nanodimensional materials including nanorobots, nanosensors for diagnosis, delivery, and sensory purposes, and actuate materials in live cells (Fig. 1). For example, a nanoparticle-based method has been developed which combined both the treatment and imaging modalities of cancer diagnosis [20]. The very first generation of nanoparticle-based therapy included lipid systems like liposomes and micelles, which are now FDA-approved [21]. These liposomes and micelles can contain inorganic nanoparticles like gold or magnetic nanoparticles [22].

The aim of the present study is to develop nanoparticle formulation of sitagliptin phosphate.

Sitagliptin Phosphate is a DPP-4 inhibitor used in the treatment of Type II Diabetes Mellitus. Sitagliptin phosphate belongs to BCS class III (high solubility and low permerability)/borderline class I high solubility and high permeability). It works competitively inhibit the enzyme DPP-4 inhibitor which breaks down the incretins GLP-1 and GIP, Gastrointestinal hormones released in response to a meal. By preventing GLP-1 and GIP inactivation, they are able to increase the secretion of insulin and suppress the release of glucagon by the pancreas. This derives blood glucose levels towards normal level. The drug is reported to cause adverse effects like abdominal pain, nausea, vomiting, degradation in gastric pH, diarrhoea, constipation, skin reactions, nasopharyngitis and pancreatitis. These conditions necessiates the formulations of nanoparticles using polymethacrylate polymers toachieve drug release in the small intestine to reduce the adverse effects and improves better patient compliance.

Nanoparticles are prepared from natural and synthetic polymers in size between 10 nm -1000 nm where the drug is dissolved, entrapped, encapsulated or attached to nanoparticle matrix. The nano sized delivery systems are able to deliver drugs to the right place at appropriate time, and at the specific dose. Advantages of nanoparticles using polymethacrylate polymers are enhanced drug absorption, decrease dose to be administered, decrease side effects, protect mucosa from irritating drugs and avoid extensive first pass metabolism.

Eudragit L 100 and Eudragit S 100 polymers are copolymer based on methacrylic acid and ethyl acrylates. The various characteristics of Eudragit L 100 and Eudragit S 100 include effective and stable enteric coatings with a fast dissolution on the upper bowel, granulation of drug substances in powder form for controlled release, site-specific drug delivery in intestine by combination with Eudragit S 100

grades. It protects the active ingredient from gastric fluid and will improve drug effectiveness.

The present study is to develop sitagliptin phosphate nanoparticles by Double Emulsion Solvent Evaporation Method (DESE) using polymethacrylate polymers such as Eudragit L 100 and Eudragit S 100 in different ratios for the treatment of diabetes mellitus.

MATERIALS AND EQUIPMENTS

Table 1 List of Materials Used

S.No.	Materials	Manufacturers
1.	Sitagliptin phosphate	Pure Chem. Pvt. Ltd. Gujarat.
2.	Eudragit L 100	Blue Fish Pharmaceuticals.
3.	Eudragit S 100	Blue Fish Pharmaceuticals.
4.	Poloxamer 188 (Pluronic F68)	Blue Fish Pharmaceuticals.
5.	Dichloromethane	Central Drug House (P) Ltd. New Delhi.
6.	Isopropyl alcohol	Merck Life Science Pvt. Ltd. Mumbai.

EXPERIMENTAL PROTOCOL

PREFORMULATION STUDY

PREPARATION OF CALIBRATION MEDIUM

Preparation of Acid Buffer pH 1.2

50ml of 0.2 M potassium chloride solution is placed in a 200ml volumetric flask.85ml of 0.2M hydrochloric acid is added and made upto the volume with distilled water.

- **Preparation of 0.2 M potassium chloride**

14.911g of potassium chloride is dissolved in distilled water and the volumeis made upto 1000ml.

- **Preparation of 0.2M hydrochloric acid**

7.292g of hydrochloric acid is diluted to 1000ml with distilled water.

Preparation of Phosphate Buffer pH 7.4

50ml of 0.2 M potassium dihydrogen phosphate solution is placed in a 200ml volumetric flask. 22.4ml of 0.2M sodium hydroxide is added and made upto the volumewith distilled water.

- **Preparation of 0.2M potassium dihydrogen phosphate**

27.218g of potassium dihydrogen phosphate is dissolved in distilled water andthe volume is made upto 1000ml.

- **Preparation of 0.2M sodium hydroxide**

8g of sodium hydroxide is dissolved and made upto 1000ml with distilled water.

ESTIMATION OF ABSORPTION MAXIMUM (λ_{max})

100mg of drug is dissolved in 100ml of acid buffer pH 1.2 and phosphate bufferpH 7.4 and after suitable dilutions and the resultant solution is scanned in the range of 200-400 nm in UV- Spectrophotometer to get absorption maximum.

PREPARATION OF STANDARD CURVE

100mg of drug is accurately weighed into 100ml standard flask and dissolved in 100ml of acid buffer pH 1.2 and phosphate buffer 7.4 separately. From this solution,10ml is taken and diluted to 100ml using acid and phosphate buffers respectively and it is designated as stock solution. From this stock solution, 5ml, 10ml, 15ml, 20ml and25ml are taken and diluted to 100ml with respective buffers so that the final concentrations of 5-25 µg/ml solutions are obtained. The above solutions are analyzedby Ultraviolet (UV) spectrophotometer at λ_{max}. Calibration curve is plotted by taking the concentration in X-axis and the absorbance in Y-axis.

DRUG-POLYMER INTERACTION STUDY

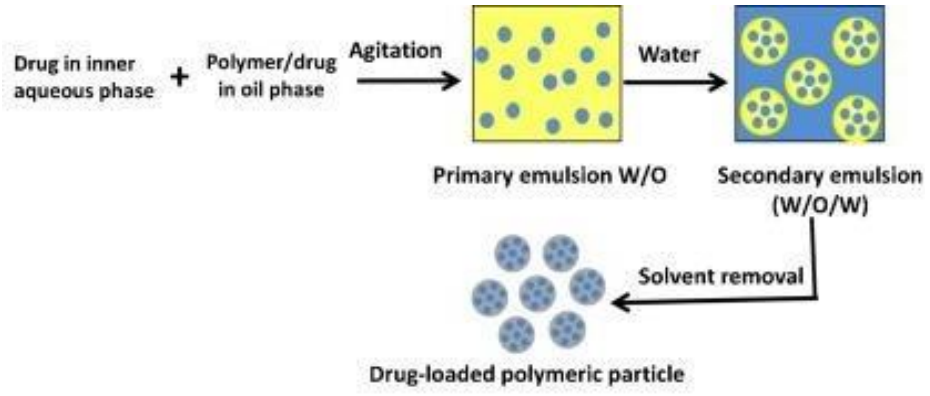
Fourier Transform- Infra Red Spectroscopy (FT-IR)

FTIR is a modern and modified form of infrared spectrometry based on mathematical formula, able to determine the structure of the drug molecule and physicalinteractions between drugs and polymers . Compatibility of drug and polymer is analyzed using FT-IR (Fourier transform infrared spectroscopy), by the potassium bromide disc method. The samples (drug, polymer and physical mixture of drug and polymer) are homogeneously mixed with potassium bromide and then compressed into pellet using hydraulic press. Each pellet is scanned in region of 4000-400 cm-1 by using FT-IR spectrophotometer and peaks are recorded and then interpreted with standard peaks .

FORMULATION OF SITAGLIPTIN PHOSPHATE NANOPARTICLES

Sitagliptin phosphate nanoparticles are prepared by Double Emulsion Solvent Evaporation (DESE) technique Polymeric solution is prepared by dissolving specific amount of polymers such as Eudragit L 100 and Eudragit S 100 in different ratios in 20ml of dichloromethane and isopropylalcohol in 1:1 ratio containing span 80 (2% v/v).Aqueous drug solution is prepared by dissolving specific amount of drug in distilled water and then followed by emulsification of this solution in polymeric solution undermagnetic stirring at 1000 – 1200 rpm for 15 min to get W/O emulsion. Further this emulsion is added to 25ml distilled water containing poloxamer 188 (1% w/v) under stirring for 10 min to achieve a stable W/O/W double emulsion and then continuously

stirred for evaporation of organic solvents. The obtained nanoparticles are filteredthrough whatsman filter paper and then dried.



Encapsulation of hydrophilic and lipophilic molecules via double emulsion techniques

Representation of Double emulsion solvent evaporation methodTable 2: Formulation of Sitagliptin Phosphate

Nanoparticles Using Eudragit L 100 in Different Ratios

FORMULATION CODE	DRUG	POLYMER (EUDRAGIT L100)	DRUG : POLYMERRATIO
F1	250mg	250mg	1:1
F2	250mg	325mg	1:1.5
F3	250mg	500mg	1:2
F4	250mg	625mg	1:2.5
F5	250mg	750mg	1:3
F6	250mg	825mg	1:3.5

Table 3: Formulation of Sitagliptin Phosphate NanoparticlesUsing Eudragit S 100 in different Ratios

FORMULATIONCODE	DRUG	POLYMER (EUDRAGIT S 100)	DRUG :POLYMER RATIO
F1	250mg	250mg	1:1
F2	250mg	325mg	1:1.5
F3	250mg	500mg	1:2
F4	250mg	625mg	1:2.5
F5	250mg	750mg	1:3
F6	250mg	825mg	1:3.5

RESULTS AND DISCUSSION

PREFORMULATION

Description :

White crystalline and odourless powder.

STANDARD CURVES FOR SITAGLIPTIN PHOSPHATE

The calibration medium (Acid buffer pH 1.2 and Phosphate buffer pH7.4) wasprepared as per IP 2014.

Estimation of absorption maximum

The λ_{max} of sitagliptin phosphate was determined by scanning the diluted concentration of drug solution in buffer solutions such as acid buffer pH 1.2 and phosphate buffer pH 7.4. It showed the λ_{max} of sitagliptin phosphate at 267nm in both buffer solutions. The results were shown in the figure

Figure 1: Determination of λ_{max} of sitagliptin phosphate using Acid Buffer pH 1.2

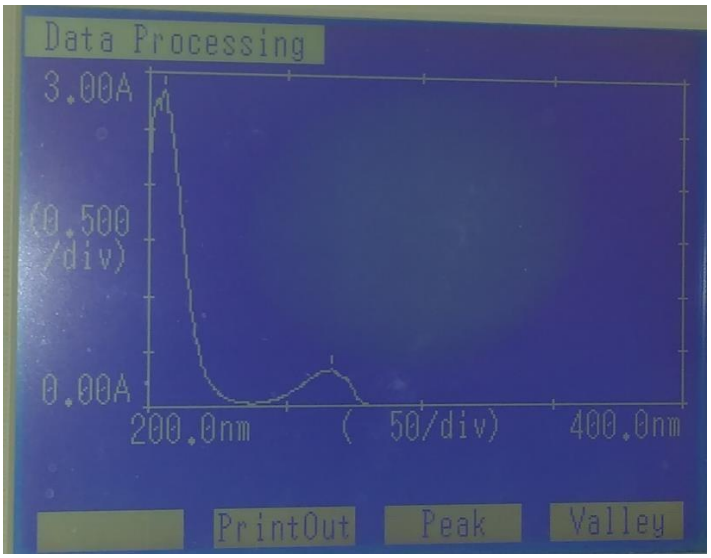
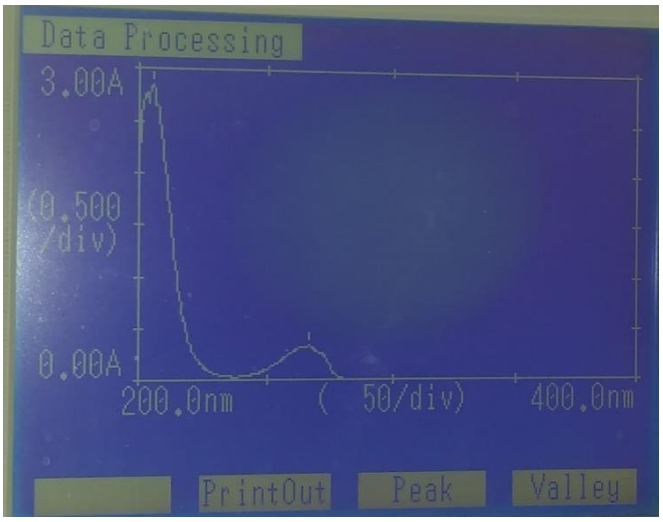


Figure 2: Determination of λ_{max} of sitagliptin phosphate usingPhosphate Buffer pH 7.4



Preparation of standard curves

The standard curves of sitagliptin phosphate prepared by using acid buffer pH 1.2 and phosphate buffer pH 7.4 were given below.

Table 4: Calibration of Sitagliptin Phosphate in Acid Buffer pH 1.2

S.No.	CONCENTRATION (µg/ml)	ABSORBANCE ±SD
1.	5	0.0183 ± 0.0004
2.	10	0.0370 ± 0.0002
3.	15	0.0552 ± 0.0002
4.	20	0.0749 ± 0.0003
5.	25	0.0965 ± 0.0003

Regression (γ) = 0.9994

Figure 3: Calibration of Sitagliptin Phosphate in Acid Buffer pH 1.2

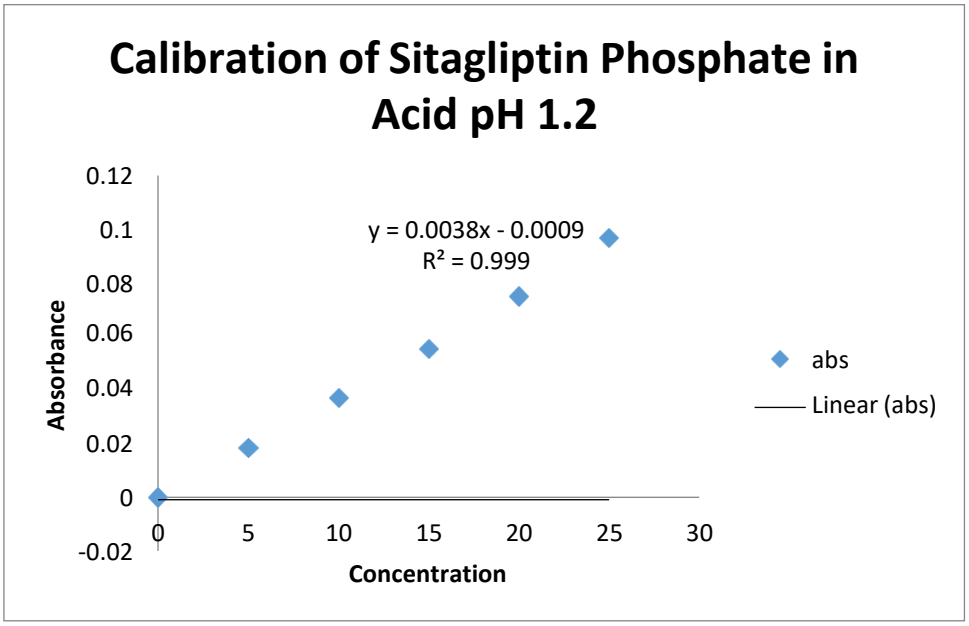
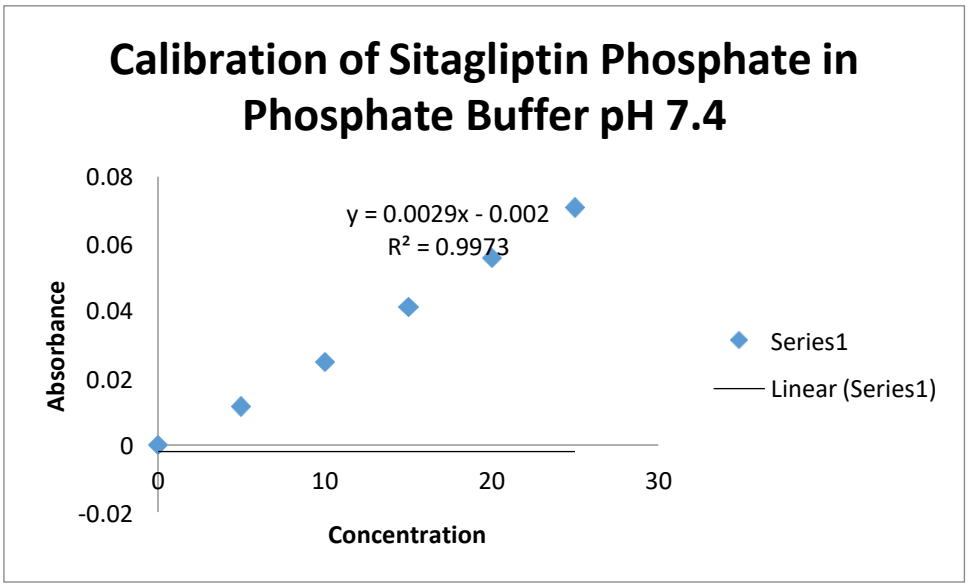


Table 5: Calibration of Sitagliptin Phosphate in Phosphate buffer pH 7.4

S.No.	CONCENTRATION (µg/ml)	ABSORBANCE ±SD
1.	5	0.0114 ± 0.0005
2.	10	0.0248 ± 0.00004
3.	15	0.0413 ± 0.001
4.	20	0.0557 ± 0.0002
5.	25	0.0708 ± 0.0005

Regression (γ) = 0.9996

Figure 4 : Calibration of Sitagliptin Phosphate Buffer pH 7.4



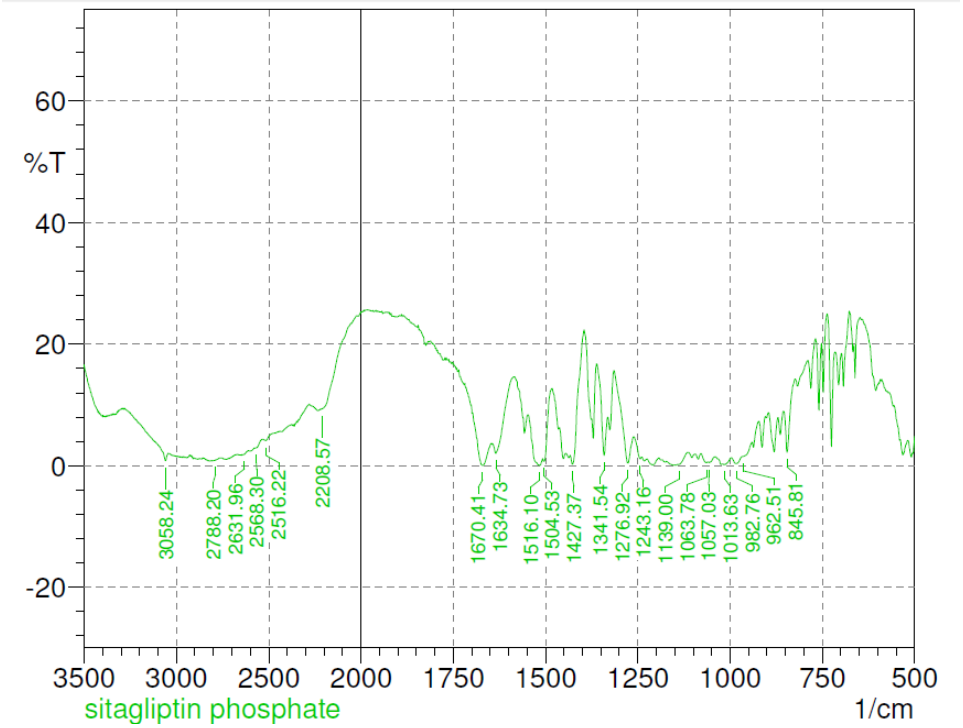
The linear correlation coefficient was obtained for calibration of sitagliptin phosphate in each medium and it obeys the Beer's law within the concentration range of 5-25µg/ml.

DRUG- POLYMER INTERACTION STUDY

Fourier Transform – Infra red Spectroscopy

The FT-IR study was conducted to determine the compatibility between the drug (sitagliptin phosphate), polymers (Eudragit L 100, Eudragit S 100), physical mixture and also the best formulation. It was found that there is no appearance or diappearance of peaks obtained from the spectrum results. The results revealed that theselected polymers were found to be compatible with the drug.

Figure 5: IR spectra of Sitagliptin Phosphate



FORMULATION OF SITAGLIPTIN PHOSPHATE NANOPARTICLES

The sitagliptin phosphate nanoparticles were prepared by using Double Emulsion Solvent Evaporation technique. Twelve formulations were prepared by usingtwo different polymers such as Eudragit L 100 and Eudragit S 100 in different ratios (1:1, 1:1.5, 1:2, 1:2.5,1 1:3, 1:3.5). Span 80 was used as a stabilizer for primary emulsion and poloxamer 188 (1% w/v) was used as a stabilizer for secondary emulsion.

CHARACTERIZATION OF SITAGLIPTIN PHOSPHATE NANOPARTICLES

Percentage yield

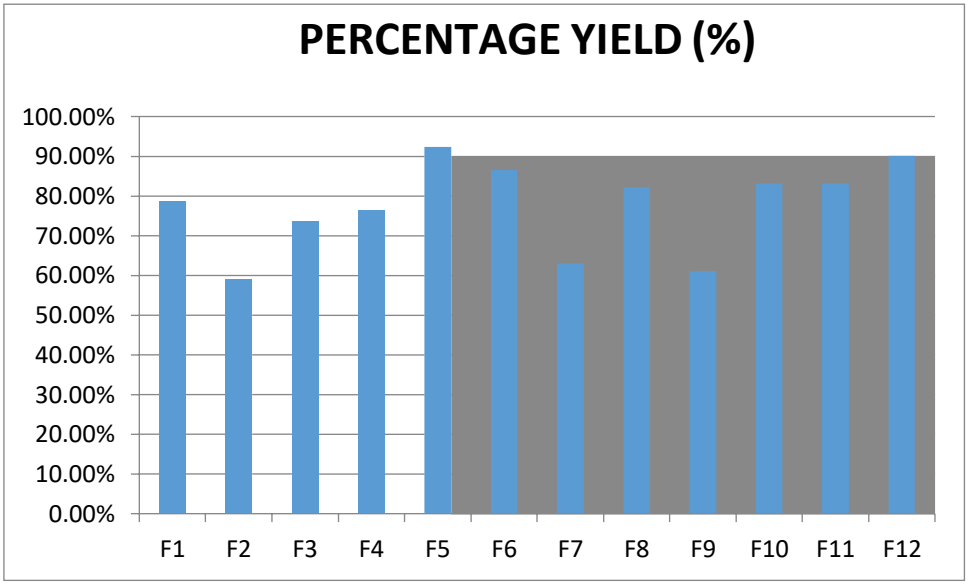
The percentage yield of obtained nanoparticles was determined by using the formula. The results were shown below

Table 6: Percentage yield of Sitagliptin Phosphate Nanoparticles

FORMULATION CODE	PERCENTAGE YIELD
F1	78.67%
F2	58.97%
F3	73.60%
F4	76.62%

F5	92.40%
F6	86.55%
F7	63%
F8	82.21%
F9	61%
F10	83.18%
F11	83.12%

Figure 6:Percentage Yield of Sitagliptin Phosphate Nanoparticles



Encapsulation efficiency and drug loading

The encapsulation efficiency of all formulations were given below

Table 7: Actual Drug Loading (%) of Sitagliptin Phosphate Nanoparticles

FORMULATION CODE	ACTUAL DRUG LOADING (%)
F1	51.85 ±0.74
F2	49.7577 ±0.18
F3	42.06 ± 0.59
F4	35.728 ±0.73
F5	26.05 ±0.31
F6	20.081 ± 0.67
F7	59.48 ±0.81
F8	52.10 ± 0.36
F9	50.34 ± 0.88

F10	36.28 ± 0.65
F11	29.47 ± 0.69

Figure 7 : Actual Drug Loading (%) of Sitagliptin Phosphate Nanoparticles

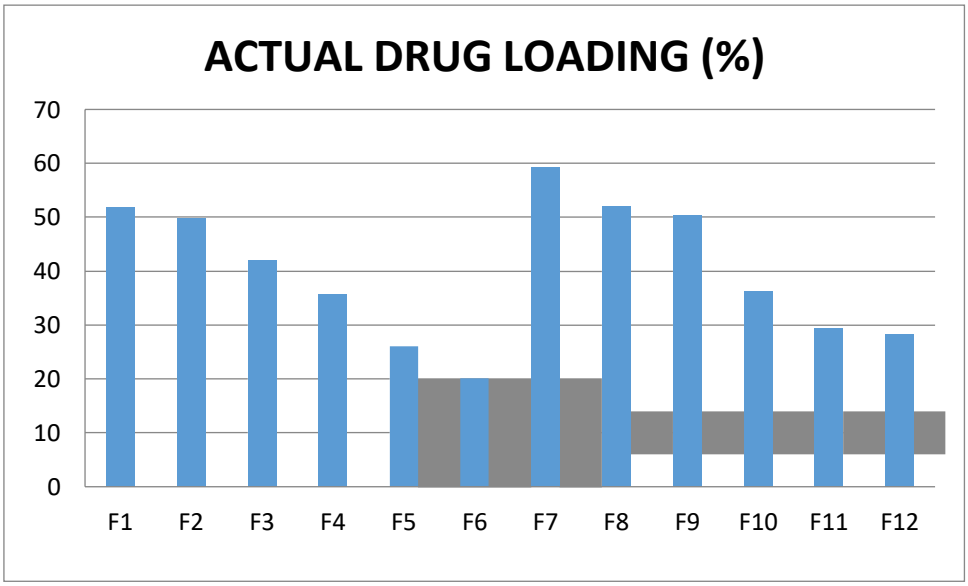
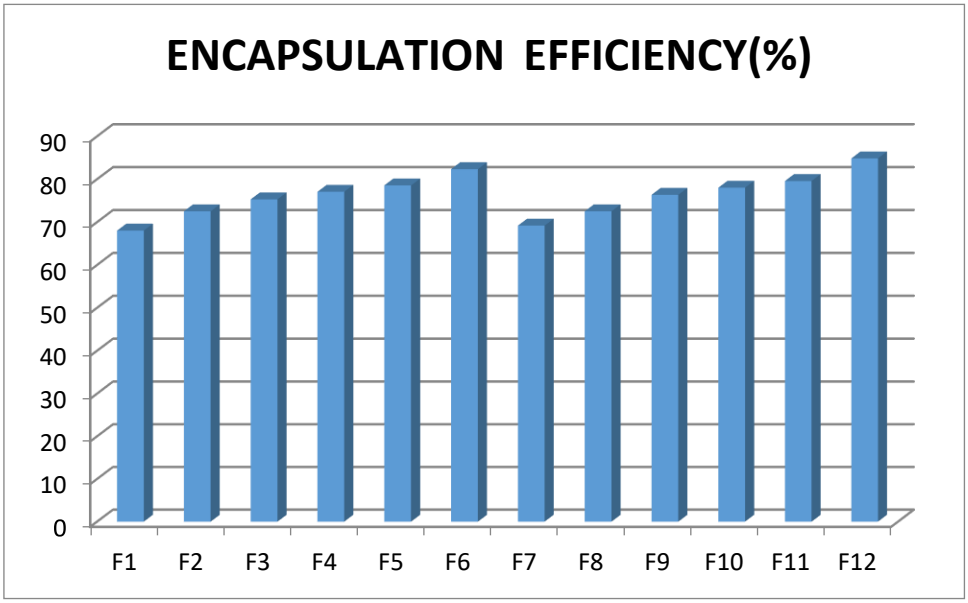


Table 8: Encapsulation Efficiency (%) of Sitagliptin Phosphate Nanoparticles

FORMULATION CODE	ENCAPSULATION EFFICIENCY (%)
F1	68.02± 0.22
F2	72.51± 0.67
F3	75.30 ±0.40
F4	77.07 ± 0.19
F5	78.55 ±0.37
F6	82.34 ±0.55
F7	69.18 ± 0.46
F8	72.51 ±0.38
F9	76.35 ± 0.45
F10	78.2 ± 0.18
F11	79.57 ± 0.09
F12	84.85 ± 0.28

Figure 8 : Encapsulation Efficiency (%) of Sitagliptin Phosphate Nanoparticles



From the results were showed above in table and figure, the drug loading of formulations (F1 to F6) using Eudragit L 100 polymer were found to be in the range of51.85% to 20.08%. The drug loading of formulation (F7 to F12) using Eudragit S 100 polymer were found to be in the range of 59.48% to 28.36%.

The encapsulation efficiency of formulations (F1 to F6) using Eudragit L 100 polymer were found to be in the range of 68.02% to 82.34%. The encapsulation efficiency of formulation (F7 to F12) using Eudragit S 100 polymer were found to be in the range of 69.18% to 84.85%.

Among all the formulations (F1 to F6), F6 showed higher encapsulation efficiency (82.34%) compared to F1 showed lower encapsulation efficiency (68.02%).

Among all the formulations (F7 to F12) F12 showed higher encapsulation efficiency (84.85%) compared to F7 showed lower encapsulation efficiency (69.18%).

The result showed that % encapsulation efficiency increases with increase in polymer concentration facilitates faster film formation across the drug which reduceddrug leaching rate from primary emulsion to secondary emulsion.

Entrapment efficiency increases where as % drug loading decreases.

***In vitro* drug release study**

The study was carried out in acid buffer pH 1.2 and phosphate buffer pH 7.4 for12hrs to mimic the *in vivo* condition. The results of *In vitro* drug release study of all formulations were shown below

Table 9: Comparison of *Invitro* Release Profile of Sitagliptin PhosphateNanoparticles Using Eudragit L 100 in Different Ratios

pH	TIME(HRS)	CUMULATIVE % DRUG RELEASE					
		F1	F2	F3	F4	F5	F6
1.2	0	0	0	0	0	0	0
	1	16.57	15.12	14.29	10.98	8.7	6.84
	2	20.71	19.68	18.5	16.94	13.55	9.348
7.4	3	25.36	24.99	25.19	22.04	20.64	23.46
	4	36.83	33.1	35.44	31.02	27.81	27.03
	5	51.08	50.05	45.46	42.2	37.46	36.97
	6	59.47	56.31	53.19	51.4	46.62	45.83
	7	62.81	60.22	62.2	60.33	55.54	57.77
	8	73.15	72.06	71.33	70.72	69.13	64.45
	9	83.57	82.43	80.51	79.53	78.9	76.31
	10	90.46	88.77	86.5	84.58	80.86	82.27
	11	95.33	93.91	91.01	90	88.2	86.16
	12	99.06	97.3	96.49	94.53	92.15	90.66

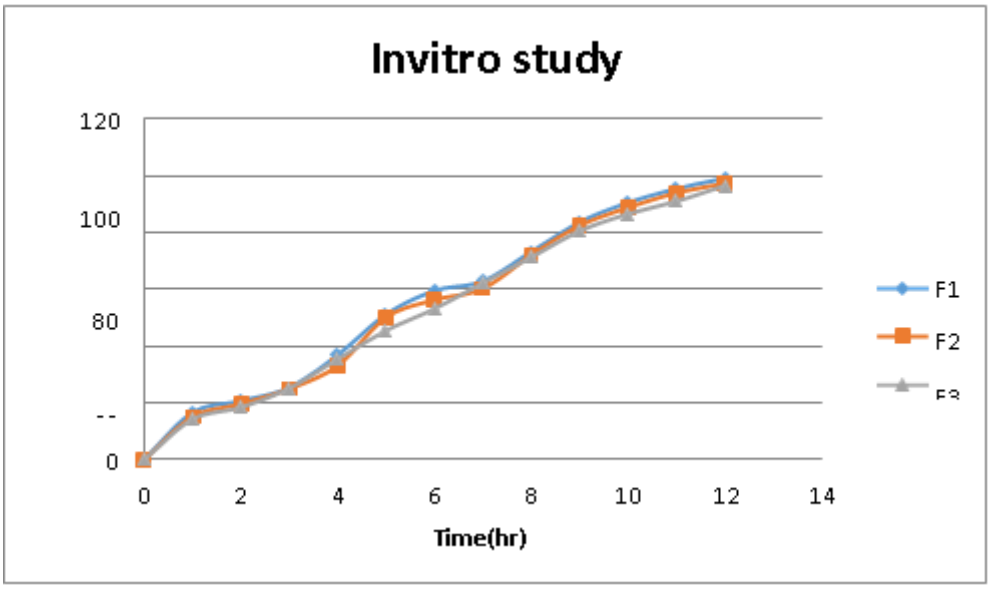


Figure 9 : Comparison of *Invitro* Release Profile of Sitagliptin PhosphateNanoparticles Using Eudragit L 100 in Different Ratios

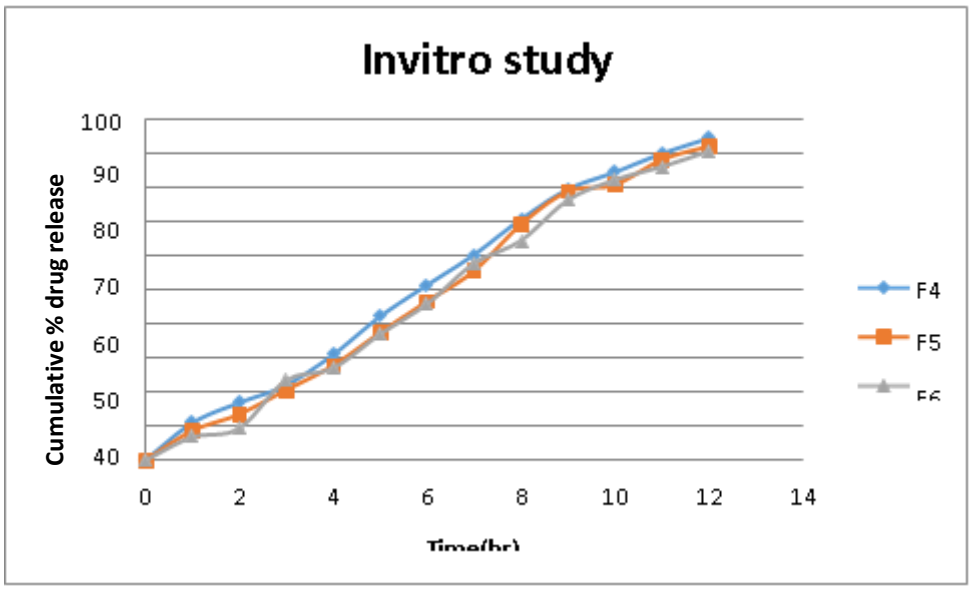


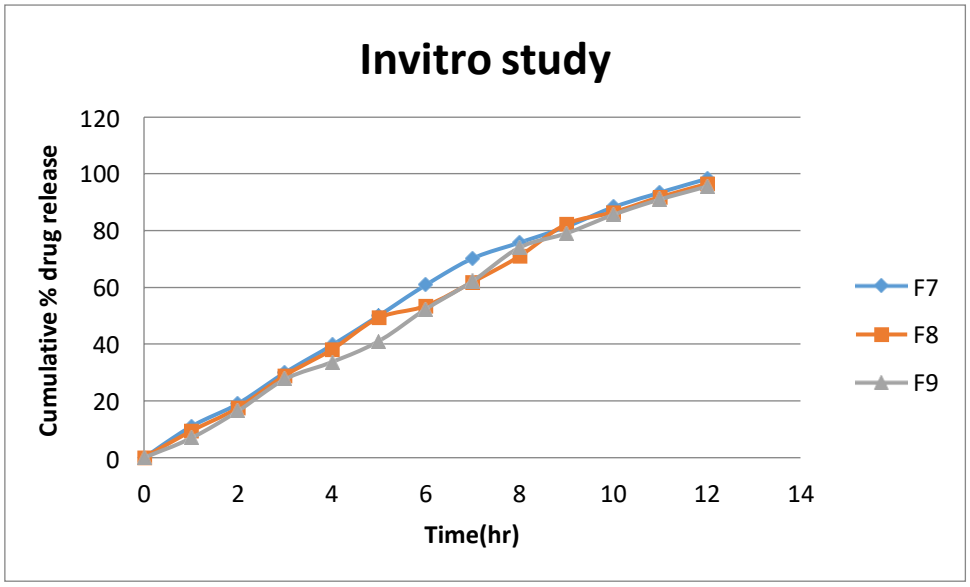
Figure 10 (B): Comparison of *Invitro* Release Profile of Sitagliptin PhosphateNanoparticles Using Eudragit L 100 in Different Ratios

Table 10: Comparison of *Invitro* Release Profile of Sitagliptin PhosphateNanoparticles Using Eudragit S 100 in Different Ratios

pH	TIME (HRS)	CUMULATIVE % DRUG RELEASE					
		F7	F8	F9	F10	F11	F12
1.2	0	0	0	0	0	0	0
	1	10.98	9.32	6.84	4.14	5.18	3.31
	2	19.01	17.51	16.39	13.4	11.57	9.43
	3	29.97	28.93	27.62	23.8	15.64	14.32
	4	39.61	38.02	33.65	30.39	27.58	23.8

7.4	5	50	49.27	40.96	38.89	33.6	31.9
	6	60.81	53.43	52.27	55.59	46.34	46.14
	7	70.21	61.85	62.13	62.23	56.2	54.49
	8	75.78	70.93	74.01	72.84	63.43	61.99
	9	81.4	82.27	79.01	79.05	74.98	69.31
	10	88.27	86.45	85.57	84.42	79.99	76.06
	11	93.45	91.82	91	88.62	87.46	85.65
	12	98.3	96.45	95.55	94.05	91.73	89.25

Figure 11: Comparison of *Invitro* Release Profile of Sitagliptin PhosphateNanoparticles Using Eudragit S 100 in Different Ratios



Formulations (F1 to F6) prepared using different concentrations of Eudragit L 100 polymer in different ratios (1:1,1:1.5, 1:2 1:2.5,1:3 1:3.5) containing 1%w/v
poloxamer showed a burst release of 20.71%, 19.68%, 18.5%, 16.94%, 13.55% and

9.34% at 2 hrs followed by sustained release of 99.06%, 97.3%, 96.49%,94.53%,

92.15% and 90.66% at 12 hours respectively.

Formulations (F7 to F12) prepared using different concentrations of Eudragit S100 polymer in different ratios (1:1,1:1.5, 1:2 1:2.5,1:3 1:3.5) containing 1%w/v poloxamer showed a burst release of 19.01%, 17.51%, 18.51%, 16.39%, 13.4%, 11.57% and 9.43% at 2 hrs followed by sustained release of 98.3%, 96.45%,

95.55%,94.05%, 91.73% and 89.25% at 12 hours respectively.

Formulation (F1 to F6) provided better drug release in the order of F6>F5>F4>F3>F2>F1 using Eudragit L 100 as polymer in different ratios.

Formulation (F7 to F12) provided better drug release in the order of F12>F11>F10>F9>F8>F7 using Eudragit S 100 as polymer in different ratios.

The initial burst release of drug was due to presence of unentrapped drug adsorbed at the nanoparticle surface followed by a sustained release due to the increasein the polymer concentration so that the release rate of drug was retarded.

The burst
effect of the drug was decreased in the formations F6 and F12 due to the increase in thepolymer concentration.

Selection of best formulation

From the above results of characterization, F6 and F12 was selected as the bestformulation. F6 and F12 were evaluated for particle size, zeta potential and polydispersity index.

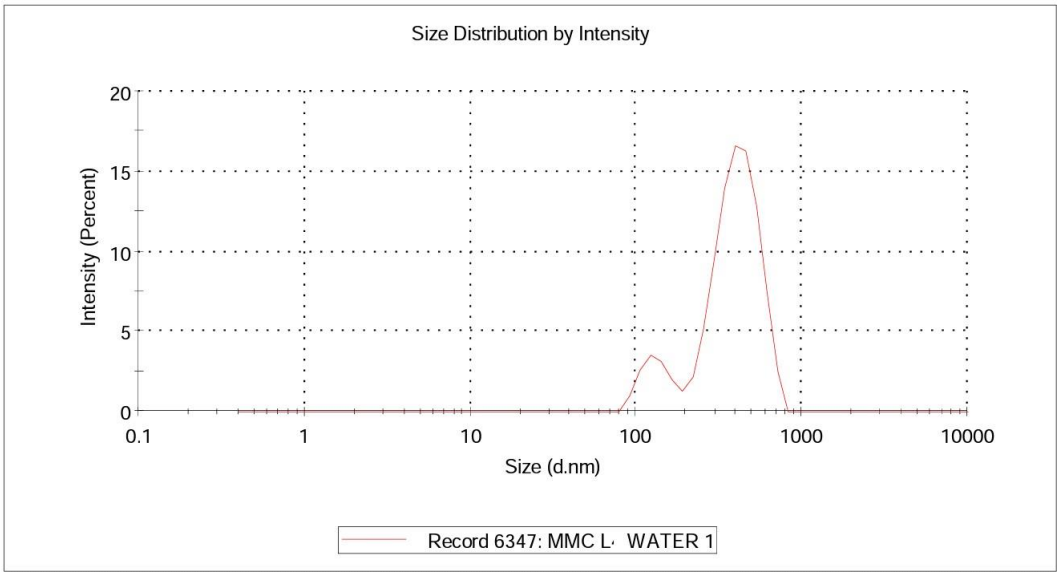
The results obtained from the reports attached, it was shown that :

Figure 13 : Particle Size and polydispersity of F6

Results

			Size (d.nm):	% Intensity:	St Dev (d.n...
Z-Average (d.nm):	458.2	Peak 1:	419.9	86.6	117.9
PdI:	0.513	Peak 2:	133.9	13.4	27.67
Intercept:	0.937	Peak 3:	0.000	0.0	0.000

Result quality : Refer to quality report



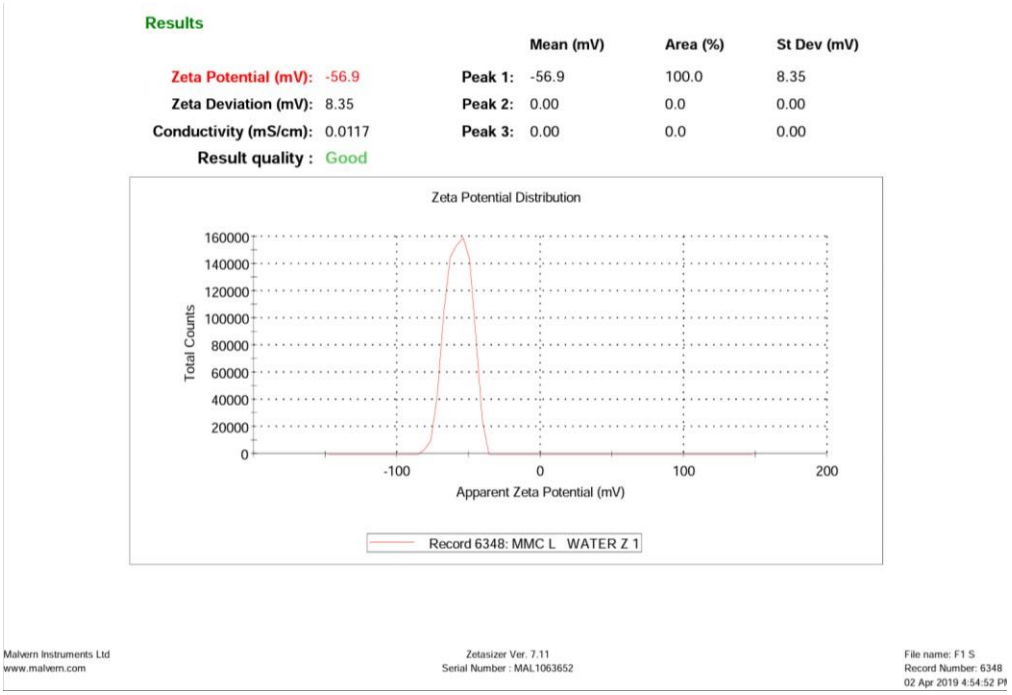


Figure 14 : Particle Size and polydispersity of F12

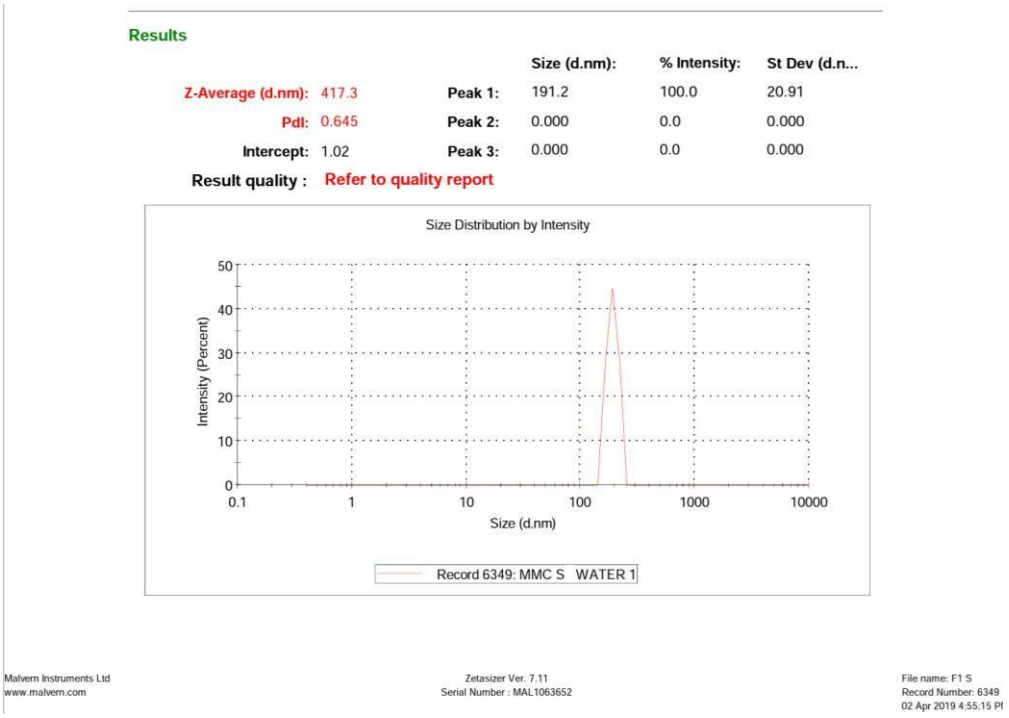


Figure 15 : Zetapotential of F12

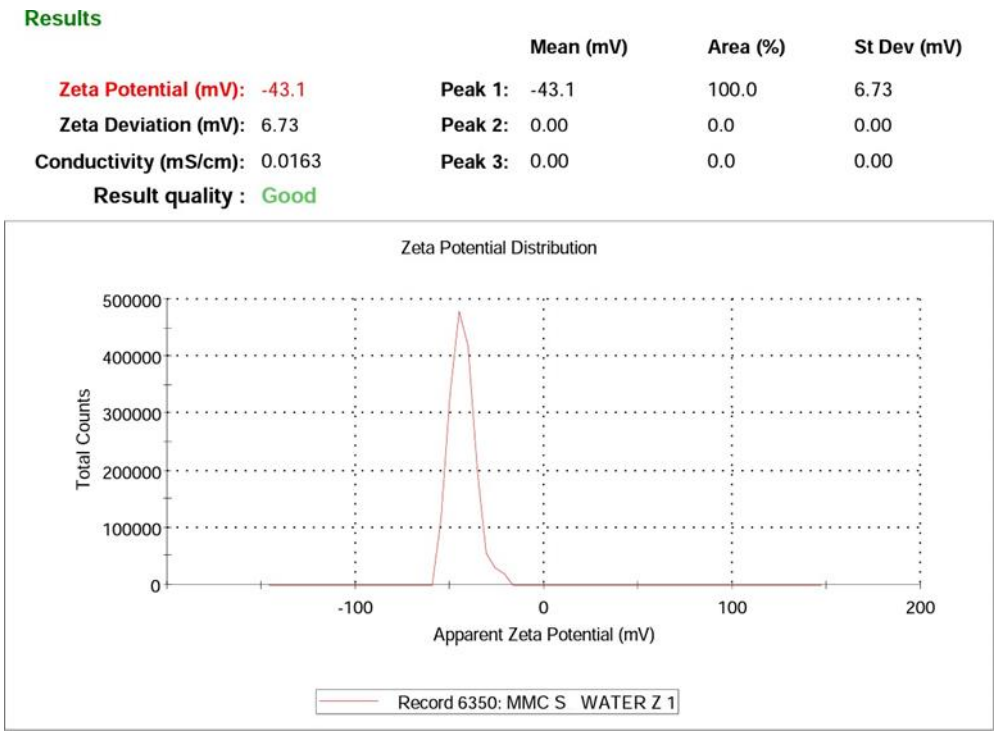


Figure 16: SEM of The Formulation F6

Formulation F6

Particle size : 458.2nm

Zeta potential : -56.9

Polydispersity index : 0.513

Formulation F12

Particle size: 417.3nm

Zeta potential : -43.1

Polydispersity index : 0.645

Zeta potential indicated that the formulations were good stability. Poly Dispersity Index values were greater than 0.5 indicated that the best formulations werehigh homogenicity.

Surface morphology:

It gives the information about the size and shape of the nanoparticles. Theresults exhibited that the nanoparticles were spherical in shape with smooth surface.

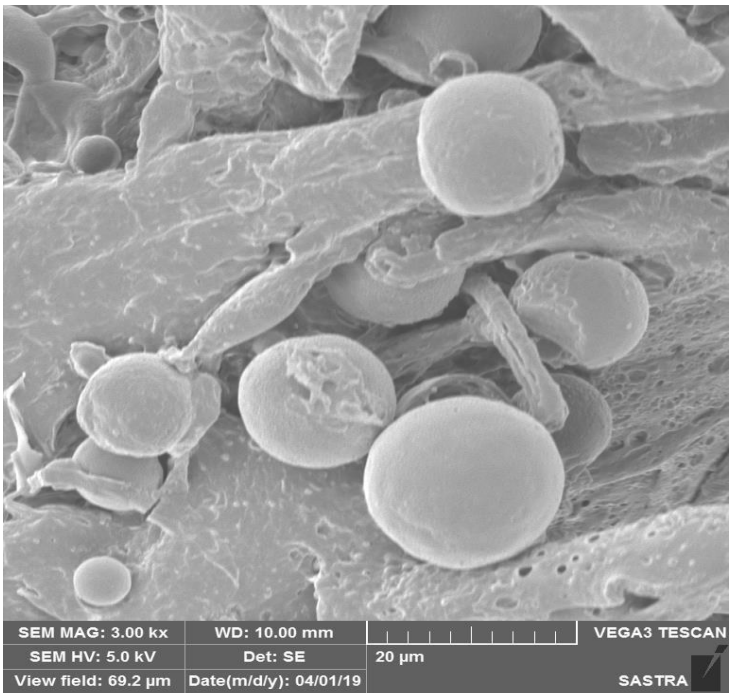
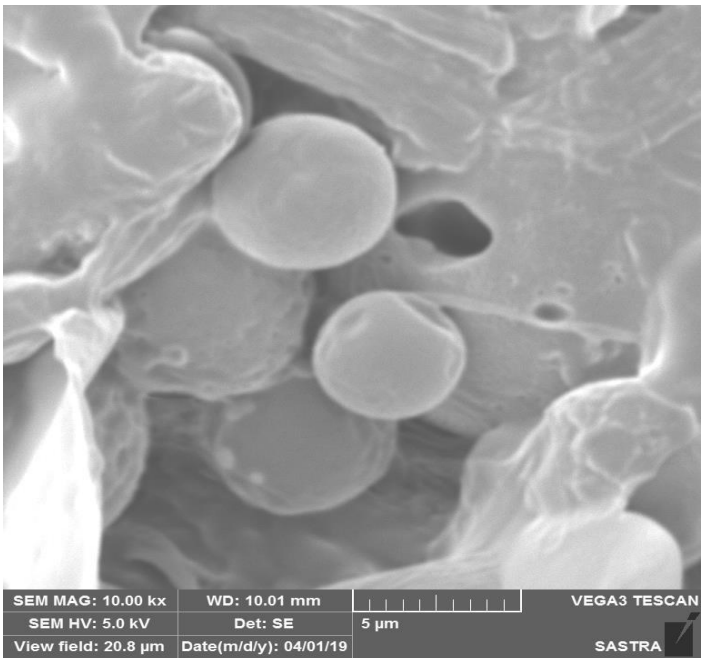


Figure 17: SEM of The Formulation F12



Drug release kinetics

Plots of zero order, first order, Higuchi, Korsmeyer – peppa and Hixcon- crowell were depicted below. The regression coefficient (r^2) were shown in figures given below . Among the models tested, the drug release profile of the best formulationwere fitted with zero order kinetics 0.99 an 0.990 respectively.

Fickian and non Fickian anomalous behaviors have been used for determining the mechanism of drug release of polymeric nanoparticles. For spheres, values of 0.5,
0.5 < n < 1.0, 1.0 and higher than 1.0 are related to Fickian diffusion, anomalous, caseII transport and super case II transport respectively.
Theresults obtained from the Korsmayer- peppas model, the values of exponent'n' were found to be 0.52 which indicated that the drug release mechanism followed non fickian diffusion.

SUMMARY AND CONCLUSION

- The present study was to formulate sitagliptin phosphate nanoparticles by using enteric coated polymers so that the drug is to be released in the small intestine for absorption , bypass the stomach, therefore to reduce side effects which results in improved better patient compliance.
- The results of FT-IR study showed that there is no interaction between the drug and the polymers.
- The sitagliptin phosphate nanoparticles were prepared by Double Emulsion Solvent Evaporation (DESE) method.
- The percentage yields, encapsulation efficiency and drug loading of all formulations were calculated.
- *Invitro* study showed that burst release of the drug was occurred in acid buffer followed by sustained release of drug for 12 hrs.
- The burst effect of the best formulations were decreased due to the polymer concentration compared to the other formulations. The best formulations were selected based on the encapsulation efficiency and *invitro* drug release study.
- F6 and F12 were showed the high encapsulation efficiency compared to the other formulations but drug loading was decreased due to the increase in the polymer concentration.
- The particle size, zeta potential, polydispersity index for the best formulations were evaluated.
- Zeta potential indicated that the nanoparticles have good stability. Polydispersity index showed that the nanoparticles size distribution have high homogenicity.
- The best formulations were fitted into Zero Order kinetic model and it followed Non Fickian Diffusion kinetics.

Hence it was concluded that the sitagliptin nanoparticles were prepared successfully by the DESE method. From the results, it was observed that the drug polymer concentration influences the encapsulation efficiency and *invitro* drug releasestudy. The nanoparticles showed that the burst release of drug on acid buffer itself andfollowed by the sustained release of the drug for 12hrs. Therefore, it could be a novel therapeutic option for the treatment of type II diabetes mellitus.

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