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Preformulation Studies of Alogliptin as Floating Microspheres for Gastroretentive Drug Delivery

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ABSTRACT

Objective: Alogliptin is a selective, orally-bioavailable, pyrimidinedione-based dipeptidyl peptidase-4 (DPP-4) inhibitor with hypoglycemic activity. Designing a new gastroretentive dosage form for alogliptin compels performing preformulation studies for drug. Therefore, the current aim of the study was to investigate some of the important physicochemical properties of alogliptin which can help to select subsequent approaches during the development of floating microspheres for oral use.

Methods: Preformulation studies of drug were carried out for identification (physical appearance, melting point and UV spectrophotometric analysis), solubility profile, lipophilicity (Partition coefficient), compatibility studies by fourier transform infrared (FTIR) spectroscopy and thermal behavior by differential scanning calorimetry (DSC).

Results: The melting point of alogliptin was found to be 187±3°C. The log P value was found to be 0.46±0.02, from which it can be interpreted that drug is highly hydrophobic in nature. The scanned λ_{max} were found to be 236 nm. No significant changes were found when FTIR spectra of physical mixture compared with FTIR spectra of pure drug and excipients. This indicates absence of any possible interaction between the drug and excipients which confirms the identity and purity of drug. DSC thermogram of pure drug showed a sharp exothermic peak at 191.923ºC (area=68.890 mJ, delta H=22.963 J/g) indicating the crystal melting point of the drug.

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Conclusion: These results suggest that the alogliptin serve as suitable candidate for gastroretentive drug delivery system.

Keywords: Alogliptin, Preformulation, Gastroretentive delivery, Spectrometric analysis, Compatibility.

INTRODUCTION

Preformulation study is an important tool for determination of physical and chemical properties of the drug prior to the development of dosage form. The nature of the drug highly affects the processing parameters like method of preparation, entrapment efficiency, compatibility and pharmacokinetic response of the formulation. Preformulation studies are indispensable protocol for development of safe, effective and stable dosage form. Thus, in order to ensure optimum condition for clinically beneficial delivery system, preformulation studies were carried out. A thorough understanding of these properties, ultimately provide a rational for formulation design. Characterization of drug and drug excipient compatibility studies were done in this phase to provide a useful support in development of dosage form[1].

Alogliptin is a selective, orally-bioavailable, pyrimidinedione-based dipeptidyl peptidase-4 (DPP-4) inhibitor with hypoglycemic activity. Alogliptin inhibits DPP-4, which normally degrades the incretins glucose-dependent insulinotropic polypeptide (GIP) and glucagon like peptide-1 (GLP-1)[2]. The inhibition of DPP-4 increases the amount of active plasma incretins which helps with glycemic control. GIP and GLP-1 stimulate glucose dependent secretion of insulin in pancreatic beta cells. GLP-1 has the additional effects of suppressing glucose dependent glucagon secretion, inducing satiety, reducing food intake, and reducing gastric emptying[3]. Alogliptin has demonstrated high selectivity to DPP-4 relative to other related serine proteases but peak inhibition of DPP-4 occurs within 2-3 hours after a single-dose administration to healthy subjects which favours the development of gastroretentive drug delivery system[4].

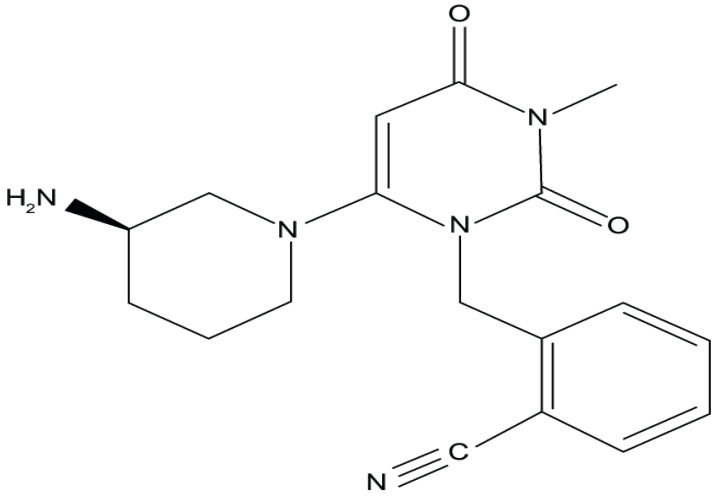

Fig. 1: Chemical structure of alogliptin[5].

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Therefore, the current aim of the study was to investigate some of the important physicochemical properties of alogliptin which can help to select subsequent approaches during the development of floating microspheres for oral use[6].

Preformulation studies were carried out for identification (physical appearance, melting point and UV spectrophotometric analysis), solubility profile, lipophilicity (n-octanol-water partition-coefficient determination), spectrometric fingerprints and compatibility studies by FTIR and thermal behavior analysis by DSC. The use of preformulation parameter maximize the chances of getting a formulation which is safe, efficacious and stable product and at the same time provide optimization of the drug product quality[7].

MATERIALS AND METHODS

Materials

The alogliptin was kindly received as a gift sample by M/s Zydus Cadila Health Care Ltd. (Ahmedabad, India). Cellulose acetate butyrate (CAB), polyethylene oxide (PEO) was a gift sample procured from Loba Chemie Pvt. Ltd. (Mumbai, India). Analytical reagent grade samples of potassium chloride, potassium dihydrogen phosphate, sodium bicarbonate, sodium chloride, magnesium chloride, ammonium carbonate, methanol, ethanol, dimethylsulphoxide, isopropyl acetate, ether, acetone and hexane were purchased from S.D Fine chemicals (Mumbai, India). Double distilled water was used throughout the work.

Methods

Organoleptic properties

Organoleptic properties of the alogliptin was characterized on the basis of appearance, color, odor and taste by visual inspection.

Melting point determination

The melting point of a drug was determined by using digital melting point apparatus (DB-31354, Decibels Instruments, Perfit, India). In this method, a tiny amount of drug was introduced into a small capillary tube, attaching this to the stem of a thermometer centered in a heating bath, heating the bath slowly, and observing the temperatures at which melting of drug begins and is completed. The melting point was recorded and compared with literature value.

Determination of solubility

Qualitative Solubility

Qualitative solubility of alogliptin in different solvent was determined according to (USP NF, 2007)[8]. Alogliptin (1 mg) was accurately weighed and transferred into a 10 ml test tube then, it was dissolved in the respective solvents (1 ml each) such as distilled water, simulated gastric fluid; SGF (pH 1.2), methanol, ethanol, dimethylsulphoxide, isopropyl acetate, ether, acetone and hexane. The solubility (mg/ml) was observed by visual inspection and compared with that available in literature.

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Quantitative Solubility

Quantitative solubility analysis of drug was done by taking 5 ml of each solvent and drug in gm(s) into the solvent till saturation of solvent. Solutions were filtered and absorbance was recorded using UV spectrophotometer and the concentration of drug dissolved in respective solvents was calculated[9]. Different solvents like distilled water and SGF (pH 1.2) were used for the solubility determination. This is done to determine the capacity of the solvent for dissolving the drug in it.

Lipophilicity (Partition coefficient)

The partition coefficient of a chemical compound provides a thermodynamic measure of its hydrophilicity-lipophilicity balance. The partition coefficient of a substance between n-octanol and water is referred to as log $P_{o/w}$, which corresponds to the negative logarithm of the ratio of the concentration of the substance in the aqueous and hydrophobic phases[10]. The partition coefficient of alogliptin was carried out in water: octanol (1:1) using shake flask procedure.

Before a partition coefficient is determined, the phases of the solvent system were mutually saturated by shaking at the temperature of the experiment. To do this, high purity analytical grade n-octanol and water were taken into a separating funnel in 1:1 ratio. Then separating funnel was shaked for 30 min. to allow complete mixing and then the funnel was allowed to stand for 24 hours to develop two phases which were saturated with each other after that the drug in minimum quantity (not more than 0.01 mol/ litre) was added to one of the phase and the funnel was again shaked for 30 minutes and then allow to stand for 1 hour after that the amount of drug in both phases (n-octanol and water) was determined spectrophotometrically.

The partition coefficient is a ratio of concentrations of unionized compound between the two solutions. To measure the partition coefficient of ionizable solutes, the pH of the aqueous phase is adjusted such that the predominant form of the compound is unionized. The logarithm of the ratio of the concentrations of unionized solute in the solvents is called log P[11,12].

$$log\ P_{oct/wat} = log\left(\frac{[solute]_{octanol}}{[solute]^{un-ionized}_{water}}\right)$$

UV-visible spectrophotometric analysis

Determination of λ_{max} of alogliptin in SGF (pH 1.2)

A standard stock solution of alogliptin was prepared by dissolving 100 mg of drug in a 100 ml volumetric flask and the volume was made upto 100 ml by using SGF (pH 1.2) to get the concentration 1000 µg/ml of standard alogliptin. From the standard stock solution, 10 ml was pipette out into 100 ml volumetric flask and the volume was made upto 100 ml with SGF (pH 1.2) to get the concentration 100 µg/ml. From this solution, 1 ml was pipette out into 10 ml volumetric flask and the volume was made upto 10 ml with SGF (pH 1.2) to get the concentration 10 µg/ml. Maximum wavelength (λ_{max}) was obtained by scanning the resulting solution (14 µg/ml) in the wavelength region between 200 nm to 400 nm by using UV-VIS spectrophotometer (UV1700 PharmaSpec, Shimadzu, Japan).

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Preparation of standard curve of alogliptin in SGF (pH 1.2)

From the above prepared stock solution, five dilutions were made by using SGF (pH 1.2) which has ultimate concentration 2 µg/ml, 4 µg/ml, 6 µg/ml, 8 µg/ml, 10 µg/ml, 12 µg/ml, 14 µg/ml, 16 µg/ml, 18 µg/ml and 20 µg/ml. Then check the pH of the diluted solutions to confirm that the diluted solutions were ranges in the pH of 1.2. The absorbance was measured at λ_{max} 236 nm by using UV-VIS spectrophotometer.

FTIR spectroscopy

FTIR spectra of the pure drug were obtained using FTIR spectrometer (FTIR-8400S spectrophotometer, Shimadzu, Japan). Sample were ground thoroughly with KBr powder in mortar and pestle, in a weight ratio of 1:100 and then pressed the mixture in dies set in pellet press under a hydraulic pressure of 15 tons for a minute. Release the pressure by rotating the side valve in anticlockwise direction to take of the pellet from the dies set. Then, the pellet was placed in the sample holder and spectral scanning was taken in the wavelength region between 4000 and 400 cm^{-1} at a resolution of 4 cm^{-1} and scan speed of 2 mm/sec[13].

Drug excipient compatibility screening by FTIR

FTIR spectra of cellulose acetate butyrate (CAB), polyethylene oxide (PEO), and a physical mixture of CAB:PEO:alogliptin in a weight ratio of 1:1:1 were obtained using FTIR spectrometer (FTIR-8400S spectrophotometer, Shimadzu, Japan). Each sample were ground thoroughly with KBr powder in a weight ratio of 1:100 and then pellets were prepared using a hydraulic pellet press under a hydraulic pressure of 15 tons for a minute. Then, the pellet was placed in the sample holder and spectral scanning were taken in the wavelength region between 4000 and 400 cm^{-1} at a resolution of 4 cm^{-1} and scan speed of 2 mm/sec. IR spectra of the physical mixture was then compared with the IR spectra of pure drug and polymer to find out the evidence of any compatibility[14].

Differential scanning calorimetric (DSC) study

DSC analysis was performed on the pure drug by using Perkin-Elmer instrument (Pyris-1, Osaka, Japan), available at Department of Textile Technology, Indian Institute of Technology, New Delhi, India. Initially, the moisture was removed by heating the samples and then, each sample (about 3-7 mg) was accurately weighed into platinum crucible 40 µl aluminium pan in hermetically sealed condition, where alpha alumina powder used as a reference. Thermograms were recorded from 50°C to 300°C at the heating rate of 20°C/min under a constant flow of an inert nitrogen gas atmosphere with the flow rate of 20 ml/min[15]. The DSC spectra used to find out the exotherm peak position or any change in their position compared with the standard spectra.

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RESULTS AND DISCUSSION

Organoleptic properties

Organoleptic properties of the drug sample were found to be as given in Table 1. The physical properties were found as similar as reported in literature that proves the identity of drug.

Table 1: Organoleptic properties of alogliptin

Organoleptic properties	*Results*
Physical form	crystalline powder
Color	White to off-white
Odor	Odorless
Taste	Tasteless

Melting point determination

The melting point of drug was determined in triplicate and their mean values with standard deviation are shown in Table 2. The melting point of alogliptin was found to be 187±3°C, which corresponds to the literature value of 185°C to 188°C that proves the identity and purity of drug.

Table 2: Melting point of alogliptin

S. No.	*Melting point (°C)*	*Mean±S.D. (°C)*
1	186	187±3°C
2	187	
3	188	

Determination of solubility

Qualitative solubility

The qualitative solubility data of alogliptin in different solvents at room temperature was shown in Table 3.

Table 3: Qualitative solubility of drug in different solvents at 37^0C

S. No.	*Solvent (1 ml)*	*Solubility of the drug (1 mg)*
1	Distilled water	Sparingly soluble
2	0.1N HCl pH 1.2	Freely soluble
3	Methanol	Freely soluble
4	Ethanol (95%)	Slightly soluble
5	Dimethylsulphoxide	Freely soluble
6	Isopropyl acetate	Very slightly soluble
7	Glacial acetic acid	Freely soluble
8	Ether	Insoluble
9	Acetone	Insoluble

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10	Hexane	Insoluble

Quantitative solubility

Results of quantitative solubility data of the drug in different solvents at room temperature was given in Table 4.

Table 4: Quantitative solubility of drug in different solvents at 37^0C

S. No.	*Solvent*	*Concentration of drug in solvent (mg/ml)*
1	Distilled water	1.02
2	0.1N HCl pH 1.2	2.13

These results indicated that the available alogliptin form is sparingly soluble in water and there is no noticeable difference between the solubility of the alogliptin form used and the solubility of the reference alogliptin.

Partition coefficient

The log P value of drug was determined in triplicate and their mean values with standard deviation are shown in Table 5. The log P value was found to be 0.46±0.02 and reported value was 0.49 from which it can be interpreted that drug is slightly hydrophobic in nature. Hence, the intestinal epithelium is expected to be the rate-limiting barrier for intestinal absorption[16]. This is an incentive to consider floating microspheres (polymeric system) for the gastroretentive delivery of alogliptin**.**

Table 5: Partition coefficient of alogliptin

S. No.	*Log P value*	*Mean±S.D.*
1	0.45	0.46±0.02
2	0.47	
3	0.48	

Standard curve of alogliptin

Determination of λ_{max} of alogliptin in SGF (pH 1.2)

UV spectrophotometric study was carried out in order to determine the λ_{max} of alogliptin in SGF (pH 1.2). λ_{max} of alogliptin was found to be 236 nm for 10 µg/ml solution as shown in Table 6. Figure 1 shows the peak at 236 nm of alogliptin in SGF (pH 1.2). The scanned λ_{max} were found to be similar as that of reported λ_{max} (236 nm).

Table 6: Scanned λ_{max} and absorbance of alogliptin in SGF (pH 1.2)

S. No.	*Strength (µg/ml)*	*Scanned λ_{max} (nm)*	*Absorbance*
1	4	340	0.045
2	6	290	0.041
3	8	270	0.032

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4	10	236	1.077
5	12	214	0.098
6	14	207	1.487

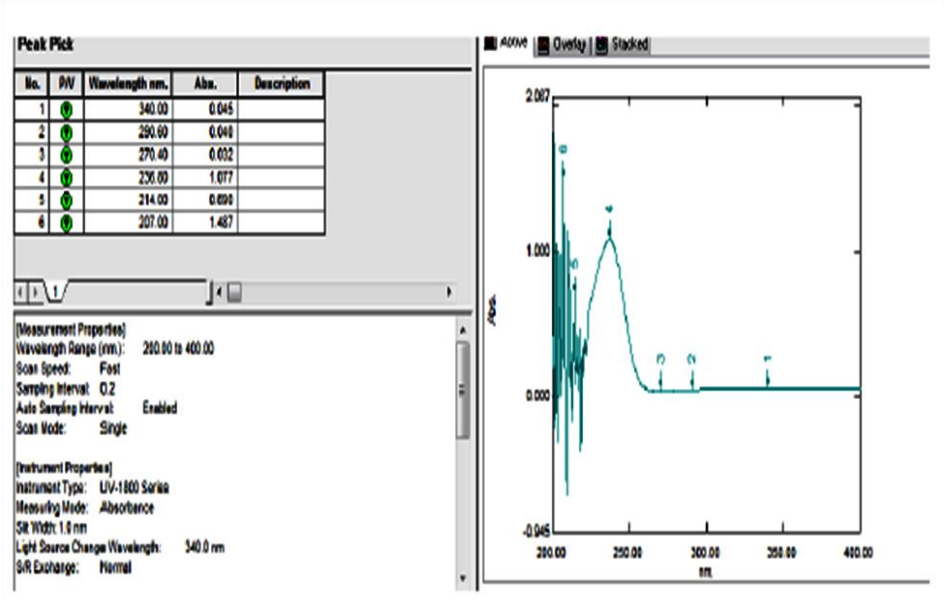

Figure 1: Peak of aloglitin in SGF of pH 1.2

Preparation of standard curve of alogliptin in SGF (pH 1.2)

The concentration and absorbance data of alogliptin in SGF (pH 1.2) were given in Table 7. This absorbance was plotted on Y-axis against concentration on X-axis and slope of the standard curve was obtained that was shown in Figure 2. The slope and intercept was found to be 0.029 and 0.003 respectively.

Table 7: Standard curve data of alogliptin in SGF (pH 1.2)

S. No.	*Concentration (µg/ml)*	*Absorbance*
1	0	0.000
2	2	0.0639
3	4	0.1255
4	6	0.1922
5	8	0.2292
6	10	0.2894
7	12	0.3547
8	14	0.4263
9	16	0.4694
10	18	0.5408
11	20	0.5926

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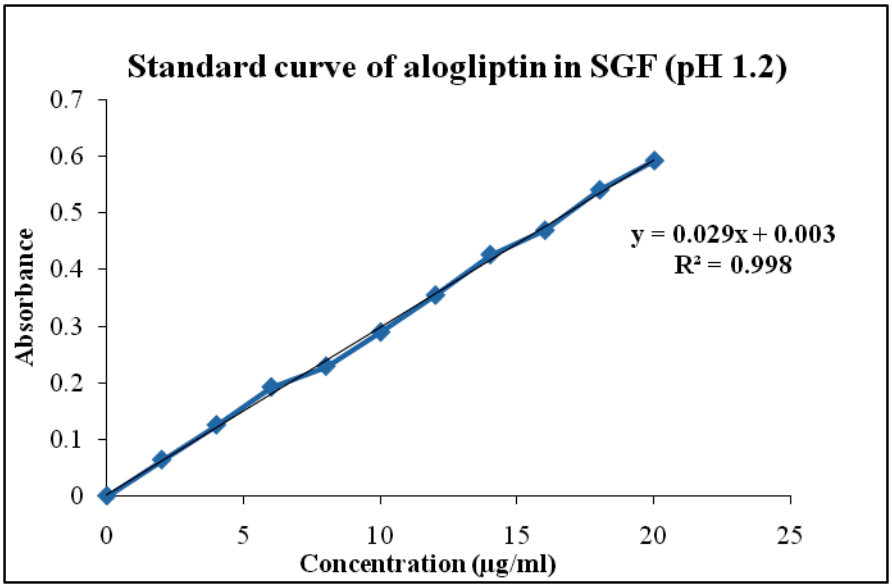

Figure 2: Standard curve of alogliptin in SGF (pH 1.2)

FTIR spectroscopy

FTIR spectra of the pure drug were obtained using FTIR spectrometer (FTIR-8400S spectrophotometer, Shimadzu, Japan) and were presented in Figure 3. The interpretation of FTIR spectra of alogliptin was shown in Table 8. Alogliptin showed the principle IR peaks at 3051.99 cm^{-1} resulted from N-H stretching, the peak at 1705.07 cm^{-1} resulted from C=O stretching, the peak at 1655.03 cm^{-1} resulted from C=N stretching, the peak at 1557.63 cm^{-1} resulted from N=H bending and the peak around 1172.39 cm^{-1}, indicating stretching of C-C group. All the principal peaks of alogliptin are present in the spectra, which confirm the purity and identity of drug.

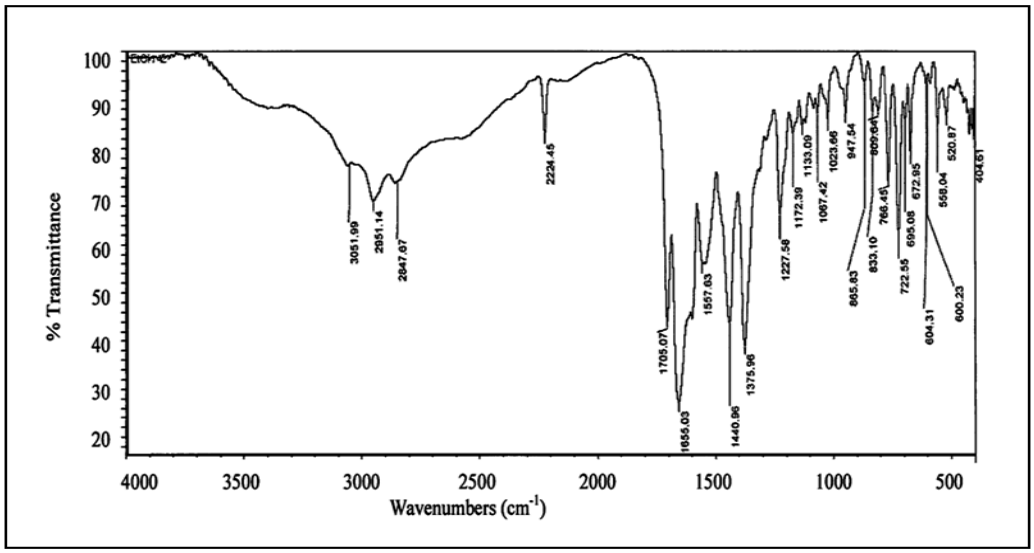

Figure 3: FTIR spectra of alogliptin

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Table 8: Interpretation of FTIR spectra of alogliptin

S. No.	*Functional group*	*Reported frequency (cm^{-1})*	*Observed frequency (cm^{-1})*
1	N-H stretching	3400-3050	3051.99
2	C=O stretching	1900-1600	1705.07
3	C=N stretching	1700-1600	1655.03
4	N=H bending	1700-1500	1557.63
5	C-H bend in plane	1500-1300	1375.96
6	C-C stretching	1200-800	1172.39
7	N-H rocking	900-700	722.55

Drug excipient compatibility screening by FTIR

FTIR spectra of cellulose acetate butyrate (CAB), polyethylene oxide (PEO) and a physical mixture of CAB: PEO: alogliptin in a weight ratio of 1:1:1 were obtained using FTIR spectrometer (FTIR-8400S spectrophotometer, Shimadzu, Japan) and was presented in Figure 4, Figure 5 and Figure 6 respectively and the interpretation of FTIR spectra was shown in Table 9, Table 10 and Table 11 respectively.

No significant changes were found when FTIR spectra of physical mixture compared with FTIR spectra of pure drug and excipients. This indicates absence of any possible interaction between the drug and excipients.

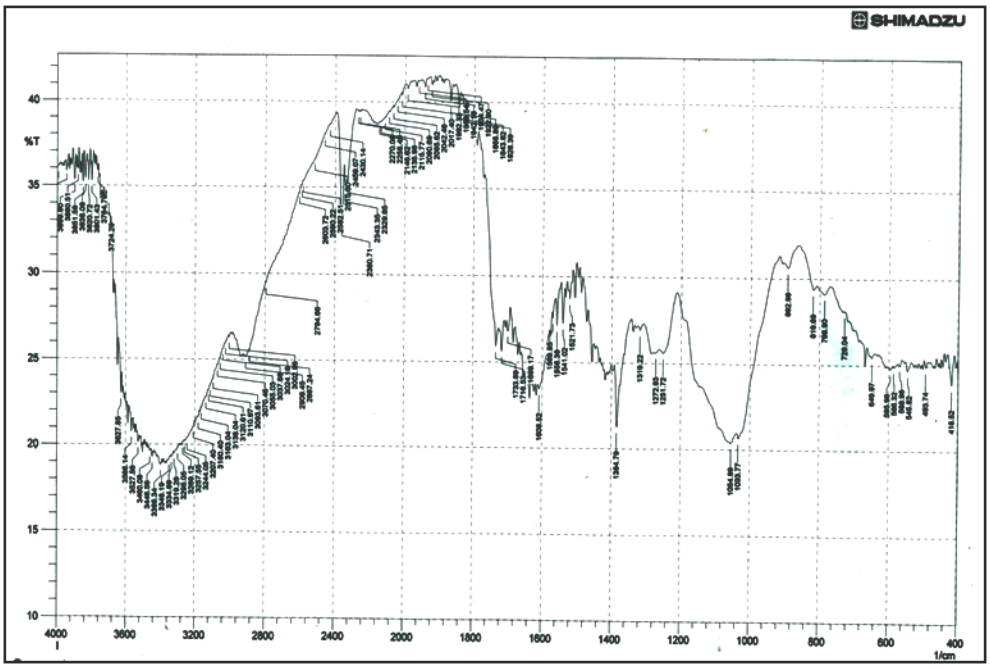

Figure 4: FTIR spectra of cellulose acetate butyrate

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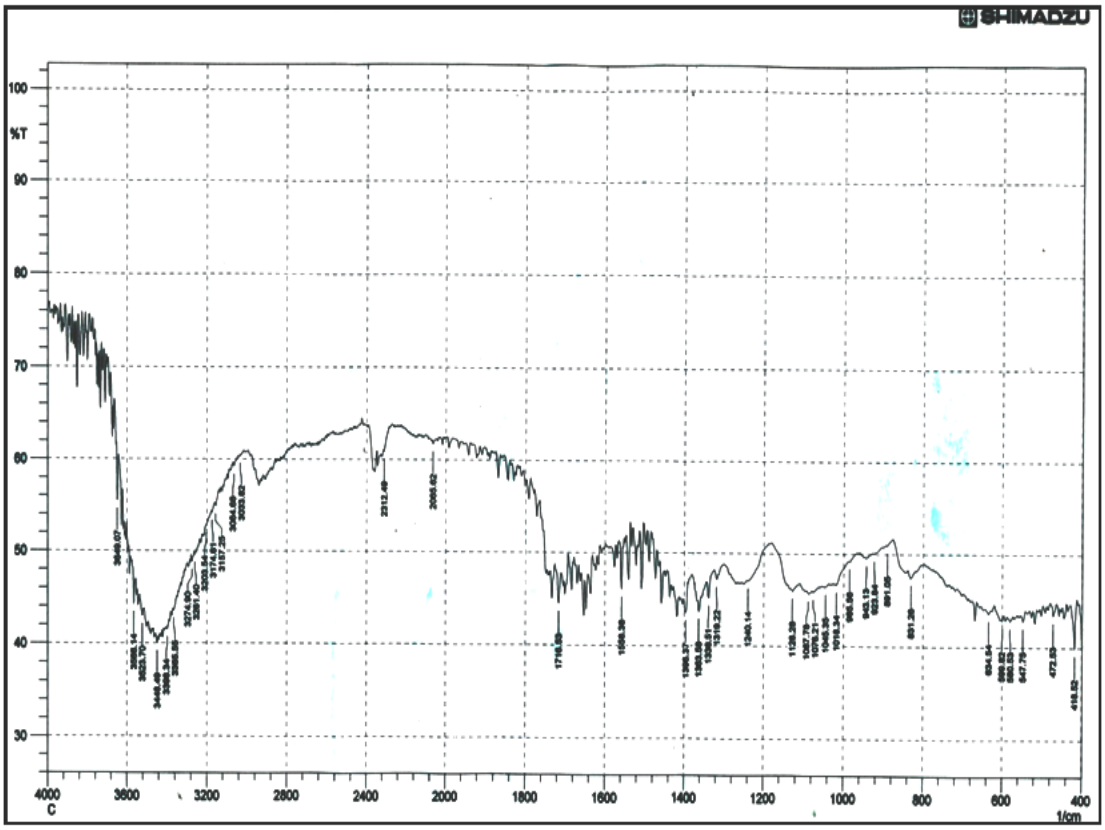

Figure 5: FTIR spectra of polyethylene oxide

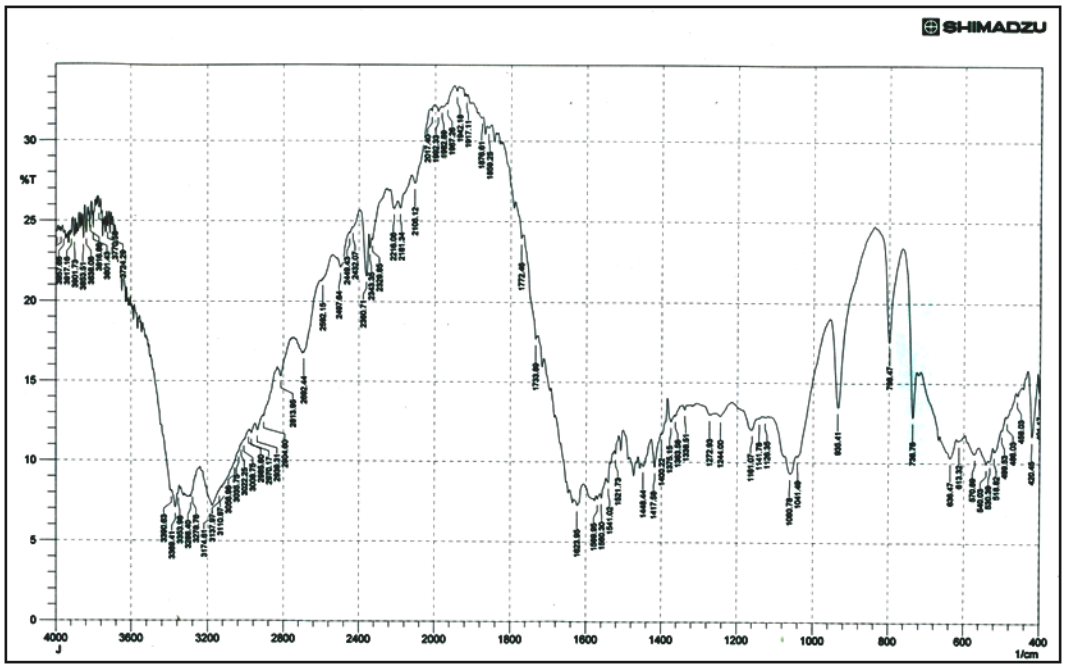

Figure 6: FTIR spectra of physical mixture

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Table 9: Interpretation of FTIR spectra of cellulose acetate butyrate

S. No.	*Functional group*	*Reported frequency (cm^{-1})*	*Observed frequency (cm^{-1})*
1	C=O stretching	1900-1600	1608.52
2	C-C stretching	1200-800	1054.99
3	C-H stretching in ring	3330-3000	3319.20
5	C-H bending	1470-1350	1384.79

Table 10: Interpretation of FTIR spectra of polyethylene oxide

S. No.	*Functional group*	*Reported frequency (cm^{-1})*	*Observed frequency (cm^{-1})*
1	C-O-C stretching in ring	1150-1000	1128.28
2	C-C stretching	1200-800	831.26
3	C-H stretching in ring	3330-3000	3274.90
4	C-H bending	1470-1350	1396.37

Table 11: Interpretation of FTIR spectra of physical mixture

S. No.	*Functional group*	*Reported frequency (cm^{-1})*	*Observed frequency (cm^{-1})*
1	N-H stretching	3400-3250	3056.96
2	N-H bending	1650-1580	1560.30
3	N-H wagging	910-665	636.47
4	C=N stretching	1700-1600	1623.95
5	C-H stretching	3000-2850	2813.95
6	C-H bending	1470-1350	1375.15
7	C=O stretching	1900-1600	1733.89
8	C-O-C stretching in ring	1150-1000	1126.35
9	C-C stretching	1200-800	1161.07

Differential scanning calorimetric (DSC) Study

DSC thermogram tracings of alogliptin was shown in Figure 7. It showed a sharp exothermic peak at 191.923ºC (area=68.890 mJ, delta H=22.963 J/g) indicating the crystal melting point of the drug. This result is in contrary to that of the reference melting point of alogliptin which is 185-188^{0}C. The marked difference between the observed melting point and the reference one is attributed to crystallization form of the drug.

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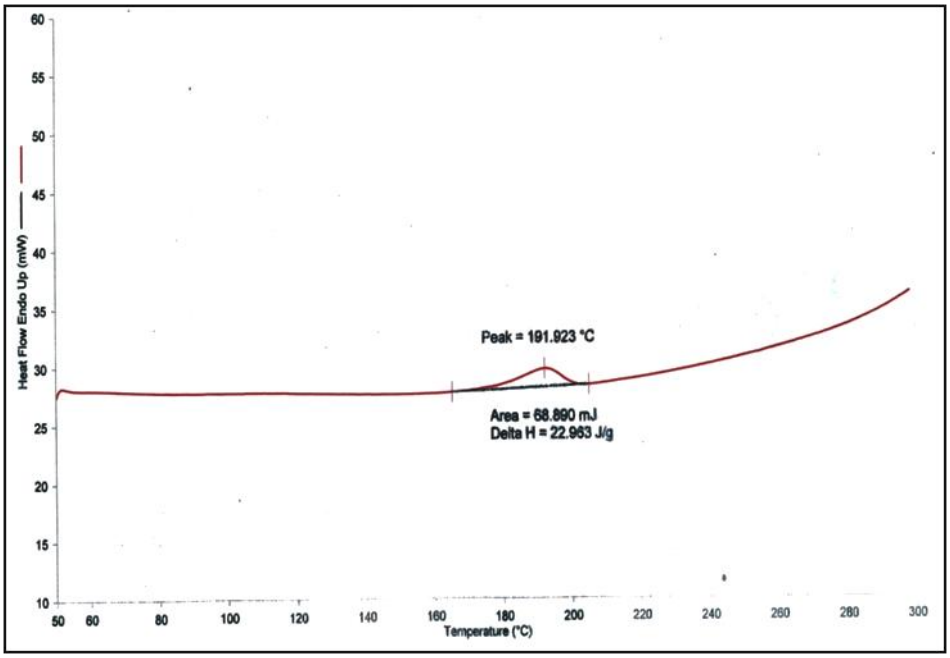

Figure 8: DSC themogram tracings of alogliptin

CONCLUSION

The preformulation parameter such as melting point and UV spectrophotometric analysis, solubility profile, partition-coefficient, spectrometric fingerprints and compatibility studies by FTIR and thermal behavior analysis by DSC; maximize the chances of getting a formulation which is safe, efficacious and stable product and at the same time provide optimization of the drug product quality. On the basis of these studies, it was concluded that the alogliptin serve as suitable candidate for floating microspheres for oral use.

LIST OF ABBREVIATIONS

DPP-4, Dipeptidyl peptidase-4; **GIP,** Glucose-dependent insulinotropic polypeptide; **GLP-1,** Glucagon like peptide-1; **CAB,** cellulose acetate butyrate**; PEO,** polyethylene oxide; **Log P,** Partition coefficient; **FTIR,** Fourier transform infrared; **DSC,** Differential scanning colorimetry; **UV,** Ultraviolet; **SGF,** Simulated gastric fluid.

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CONFLICT OF INTEREST

The authors report no conflicts of interest.

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