CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
SJIF Impact Factor: 7.187

Available online at: http://www.iajps.com Research Article

FORMULATION AND EVALUATION OF SITAGLIPTIN PHOSPHATE LOADED ORAL POLYMERIC FLOATING MICROBEADS

Bhavana Singh and Saranjit Singha*

School of Pharmaceutical Sciences, Shri Guru Ram Rai University, Patel Nagar, Dehradun, Uttrakhand, 248001, India.

Article Received: October 2021 **Accepted:** October 2021 **Published:** November 2021

Abstract:

The objective of present investigation is to prepare and optimize an oral floating alginate gel beads of Sitagliptin phosphate using sodium alginate and oils as a dispersed phase to generate a uniform emulsion to create multiple tiny chambers in the alginate matrix for better buoyancy. Sitagliptin phosphate loaded beads were prepared by emulsion gelatin method. In this method pre gelation liquid of sodium alginate solution (2-4% w/v) was prepared. Oil (olive oil) in the concentration 30%, was then added to the polymer solution. From the results formulation F-3, F-7 and F-8 was chosen as the most optimized formulation as it possessed all the required physicochemical characters and sustained drug release. The in vitro release data fitted with higher values in matrix model and the release was found to be Non- Fickian diffusion (anomalous transport) as the n value is in between 0.5 to 1. Entrapment efficiency and drug release of optimized batch F-3, F-7 and F-8 was found to be 78.22% and 92.63% respectively. Drug absorption from the gastrointestinal tract is highly variable process and prolonging gastric retention of the dosage form is a challenging task. Under such circumstances, floating drug delivery system proves to be promising approach for gastric retention. The optimization of floating, drug entrapment efficiency and drug release behaviour of Sitagliptin phosphate beads was done by applying design expert.

Corresponding author:

Saranjit Singha,

School of Pharmaceutical Sciences,
Shri Guru Ram Rai University, Patel Nagar, Dehradun,
Uttrakhand, 248001, India.

QR code

Please cite this article in press Bhavana Singh and Saranjit Singha, ***Formulation And Evaluation Of Sitagliptin Phosphate Loaded Oral Polymeric Floating Microbeads,*** *Indo Am. J. P. Sci, 2021; 08(11).*

INTRODUCTION:

A sustained release drug delivery system is known to provide a prompt release of the drug. So, to achieve and maintain the drug concentration within a therapeutically effective range needed for treatment, it is often essential to take this type of drug delivery system several times a day, which results in a significant fluctuation in drug levels [1]. For many drug substances, conventional immediate-release formulations provide clinically effective therapy while maintaining the required balance of pharmacokinetic and pharmacodynamics profiles with an acceptable level of safety to the patient. Micro-particulate drug delivery systems have various well-known advantages over single unit dosage forms [2,3,4].

Microbeads are nearly spherical, small with diameter of 0.5- 1000 µm. The solid and free-flowing particulate carriers containing dispersed drug particles either in solution or crystalline form allow a sustained release or multiple release profiles of treatment with various active agents without major side effects [5,6]. Additionally, the microbeads maintain functionality under physiological conditions, can incorporate drugs to deliver locally at high concentration, ensuring that therapeutic levels are reached at the target site while reducing the side effects by keeping systemic concentration low. The microbeads are produced from several polymers such as cationic polymers, e.g., chitosan, anionic polymers, e.g., sodium alginate, and binding components, e.g., gelatine, chondroitin sulphate, avidin in a predetermined ratio [7]. Microencapsulation has become a common technique in the production of controlled release dosage forms. One approach for the controlled release formulation of different therapeutic agents in the production of polymeric gel beads. The beads are discrete spherical microcapsules that serve as the solid substrate on which the drug is coated or encapsulated in the core of the beads [8,9]. Beads can provide sustained-release properties and a more uniform distribution of drugs within the gastrointestinal tract. Furthermore, the bioavailability of drugs formulated in beads has been enhanced. Numerous studies have been reported concerning the use of alginate beads as a controlled release carrier [10,11].

MATERIALS AND METHOD:

Materials

Sitagliptin Phosphate was obtained as a gift sample from GVS Bliss Pharma Palghar(India). HPMC, EudragitS100, Sodium Alginate, Calcium Chloride, bought from Central Dug House Pvt. Ltd. All the chemicals and reagents used in the study were of analytical grade.

Preparation of microbeads

Sitagliptin phosphate micro beads are prepared by emulsion gelation method. Sodium Alginate (4%) was dissolved in distilled demineralised water with agitation. Sitagliptin phosphate and different concentrations of mineral oil are added to the solution. This solution (2.5g) containing Sitagliptin phosphate (125 mg) and oil (0-40% (w/w)) is dropped through 21 G needle in to 1%calcium chloride (10 ml) and left at room temperature for 2 h.The resultant hydro gel beads are washed twice with distilled water and kept for drying at room temperature up to 12 hours.

Preformulation studies

Preformulation testing is the first step in the rational development of dosage forms of a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The overall objective of pre-formulation testing is to generate information useful to the formulator in developing stable and bio available dosage forms that can be man produced. The following preformulation studies are carried out:

Organoleptic properties

The colour, odor and taste of the drug were characterised and recorded. The results are shown in table

Determination of melting point

Melting point of drugs was determined by using capillary rise method by melting point apparatus, a small quantity of drug was filled in capillary tube which was sealed at one end and was placed in meting point apparatus along with the thermometer on another slot, and temperature at which the drug started melting and at which it completely melted was observed.

Solubility

The solubility of drug was determined in different solvent systems. Sufficient amount of the drug was added to 5 ml of each solvent in a volumetric flask and shaken. The samples were kept in room temperature for 24 hours. Then the samples were filtered, diluted and examined for the absence or presence of drug particles.

Determination of partition coefficient

A saturated solution of the drug in 30 ml of pH 7.4 phosphate buffer was made and absorbance was

taken after sufficient dilution. After this the saturated solution was poured into the separating funnel and 30 ml of n-octanol was added into this. This mixture was shaken for 30 min and then was kept a side for 20 min to separate both the layer. Finally, the aqueous layer was separated out and absorbance was taken and concentration was calculated.

Fourier transform infrared (FTIR) spectral analysis

FT-IR is used to identify the functional groups in the molecule. The drug is mixed with KBr and pellet is formed. Each KBr disk was scanned at 4 mm/s at a resolution of 2 cm over a wave number region of 400 to 4,500 cm−1. The characteristic peaks were recorded. The results are shown in the following figure. and table.

Finding the absorption maxima (λ max)

Appropriate dilution of Sitagliptin phosphate drug sample was prepared from the standard stock solution. Using UV Spectrophotometer, the diluted sample was scanned over the range of 200-400 nm and the λmax was determined. The spectrum of Sitagliptin phosphate is shown in figure .

Drug-Excipient Compatibility studies by FT-IR

Fourier infrared spectroscopy (FT-IR) analysis was performed for the pure drug and physical admixtures (Polymers, excipients) individually and then the drug and physical admixtures are mixed together and FT-IR is taken to find out that there is no interaction between drug, polymers and the excipients. The results are shown in the following figure.

Characterization of floating alginate beads

Physical Appearance and Morphological Analysis

All the batches of Sitagliptin phosphate beads were studied for colour and physical appearance. Surface and cross-sectional morphologies of beads were examined with a Scanning Electron Microscope (Wadia Institute of Technology Dehradun, Uttarakhand)**.** Beads were mounted on metal grids using double-sided tape and coated with gold under vacuum.

Size Analysis

The size of the 10 prepared floating alginate beads was measured by ocular microscope. Least count of the instrument was found to be 0.01mm.

Buoyancy

The floating ability was determined using USP dissolution test apparatus I (Basket method). Fifty beads were introduced in the vessels and the Basket were rotated at 100 rpm in 900 ml of 0.1 N HCl, maintained at 37±0.5 °C for 10 hr. The floating ability of the beads was observed visually. The preparation was considered to have buoyancy only when all beads floated on the test solution for the prescribed time period.The experiment was conducted thrice.

Bead Water Uptake

Bead water uptake in this case was presented as normalized weight gain ratio as defined below:

Y = mw/md

Where Y is the normalized weight gain ratio, mw the bead weight after swelling (including water uptake), and md is the initial dry bead weight. Weight gain ratio at equilibrium, Y of different floated formulations is the average of three determinations.

% Yield

% Yield for the different formulations was calculated by the formula given below,

% Yield =Total weight of floating beads produced × 100 / Total weight of drug and polymer

% Drug entrapment

50 mg of prepared floating alginate beads of Sitagliptin phosphate were dissolved in 50 ml of 0.1NHCl (pH 1.2) and the drug content was analyzed at 265 nm using a UV/visible spectrophotometer (Shimadzu-1800). Encapsulation efficiency was calculated as the percentage (w/w) of the theoretical drug content.

% Drug Entrapment = (Actual drug content /Theoretical drug content) x 100

***In Vitro* Drug Release Studies**

The *in vitro* drug release studies of different formulations (F-1, F-7, and F-8) were conducted to ensure the effect of sodium alginate concentration, calcium chloride concentration and drug loading concentration on the release of Sitagliptin phosphate from the formulations. The *in vitro* dissolution studies of the floating formulations were carried out using USP dissolution test apparatus I (basket method). The basket of USP dissolution test apparatus I, each containing an amount of beads equivalent to 250 mg Sitagliptin phosphate, were rotated at 100 rpm in 900 ml of 0.1N HCl maintained at 37°C±0.5 °C. An aliquot of 10 ml of the solution was withdrawn at predetermined time intervals and replaced by fresh dissolution medium. The withdrawn samples were analyzed for Sitagliptin phosphate content spectrophotometrically at max 265 nm.

Drug release kinetic data analysis

Several kinetic models have been proposed to describe the release characteristics of a drug from the matrix, these are as following

Zero order kinetics

When a graph of the cumulative percentage of the drug released from the matrix against time is plotted, zero order is linear in such plot, indicating that the release rate is in-dependent of concentration.

$Q_t = Q_0 + k_0 t$

Where, $Q_0$is the initial amount of the drug in the dosage form, $Q_t$is amount of drug in the dosage form at time t andk_0 is zero order rate constant.

First order kinetics

$Q_t = Q_0 e^{-kt}$ or $\ln Q_t = \ln Q_0 + kt$

Where, $Q_t$is the amount of the drug released in time t, Q_0 is the initial amount of the drug in the solution and k is first order rate constant.

Higuchi Model:

$Q_t = K_H t^{1/2}$

Where, Q_t is the amount of the drug released in time t, and K_H is Higuchi dissolution constant.

Koresmeyer-Peppas Model:

$Q_t = K_p t^n$ or $\log Q_t = \log K_p + n \log t$

Where, Q_t is the amount of the drug released in time t, K_p is Koresmeyer-peppas release

rate constant and n is the diffusion exponent.

The release rate constants k and n of each model were calculated by linear regression analysis Coefficient of determination (r^2) was used to evaluate the accuracy of fit.

Hixson-Crowell Model

Hixson and Crowell (1931) recognized that the particle regular area is proportional to the cubic root of its volume derived an equation that can be described in the following manner.

$W_0 1/3 - W_t 1/3 = K_s t$

Where, W_0 is the initial amount of drug in pharmaceutical dosage form, W_t is the remaining amount of the drug at time t in dosage form and $K_s$is an s constant incorporating the surface volume relation. This relation applies to pharmaceutical dosage form such as tablet. (Costa & Sousa 2001)

RESULTS AND DISCUSSION:

The present work involves the formulation and evaluation of Sitagliptin phosphate loaded oral polymeric floating microbeads. In this formulation HPMC and Eudragit was used as polymers to achieved sustain drug release, Calcium chloride was used as a cross linking agent which will form a complex with the polymers used and olive oil was used to enhanced the yield of the microbeads.

Organoleptic properties

From the given data in table no.3, it was observed that the organoleptic properties of test drug matches with the given standard data. This can be used as preliminary identification tool for drug. Shown in table no.1

Melting point, Solubiliy and Partition coefficient

The melting point of sitagliptin phosphate drug sample was found to be 201°C, which is in range. It is found to be freely soluble in deionized water, 0.1N HCl and pH 6.8 Phosphate Buffer. Shown in table no.2. and 3 respectively.The partition coefficient of Sitagliptin phosphate was found to be 1.26. The reported valve of partition coefficient is 1.95.

Absorption maxima (λ max)

It was found that the Sitagliptin phosphate drug sample showed maximum absorbance at 265 nm, which was selected as the wavelength for detection. Given below in figure

Fourier transform infrared (FTIR) spectral analysis

The compatibility study was carried out to study the possible interaction between Sitagliptin phosphate and other excipients. The IR spectrum of pure Sitagliptin phosphate and other excipients was compared with the IR spectrum of pure Sitagliptin phosphate. The IR spectrum of drug-excipients were matching with the IR spectrum of pure Sitagliptin phosphate. There is no appearance or disappearance of characteristic peaks, indicating compatibility between drug and other excipients. Given below in figure

CHARACTERIZATION OF FLOATING ALGINATE BEADS

Physical Appearance, Morphological Analysis, Size Analysis and Buoyancy

The color of the prepared beads are of creamy white and round or either oval in shape. The size of the 10 prepared floating alginate beads was measured by ocular microscope. Least count of the instrument was found to be 0.01mm. The average size ranges between 1.440 to 1.572 ± 0.076mm. Results show that by the increase in concentration of sodium alginate, the mean particle size of microbeads increased. Thus, larger microbeads were obtained by increasing the concentration of sodium alginate. It was found that, the formulation F-1, F-6, F-7 and F-8

continued floating more than 8 hrs. The formulation F2, F5, F10 and F13 did not come over the surface of the applied suitable solvent. Shown in table no.5.

% Yield, % Drug entrapment, Drug content uniformity and Bead Water Uptake

Among all the formulation, the% Yield of the best three formulation i.e., F-1, F-7 and F-8 found to be 94.23%, 96.44% and 98.24% respectively. The % Drug Entrapment of F-1, F-7 and F-8 was found to be 85.6, 95.2 and 98.4% respectively, which is the highest among all other formulation. The mean Drug content uniformity of the best three formulation i.e. F-1, F-7 and F-8 was found to be 92.37± 0.25, 85.79± 0.56 and 96.75± 0.25 respectively. The beads water uptake of all formulation was ranges between 0.284±0.00244 and 0.6423± 0.0007 mg. Shown in table no.6.

Table no.1: Organoleptic properties of drug

S. No.	Parameters	Observation
1	Description	Crystalline powder
2	Colour	White to off-white
3	Odour	Odourless
4	Taste	Tasteless

Table no.2: Melting Point Determination of Drug

S.No.	Observed melting point	Average melting point	Standard melting point
1	203°C	201°C	198°C-202°C
2	199°C		
3	201°C		

Table no.3: Solubility of Drug in Different Solvents

S.No.	Solvents	Concentration (µg/ml)
1	Deionized water	9.59
2	0.1 N HCl	7.78
3	pH 6.8 Phosphate buffer	6.45

Table no.3: Formulation table of HPMC beads

Ingredients	HPMC beads formulation code						
	F1	F2	F3	F4	F5	F6	F7
Drug (mg)	10	10	10	10	10	10	10
HPMC (mg)	200	200	200	200	200	200	200
Sodium alginate (%)	6	4	4	4	6	6	4
Calcium chloride (%)	2	1	2	1	1	2	2
Olive oil (ml)	1	0.5	0.5	1	1	0.5	1

Table no.4: Formulation table of Eudragit beads

Ingredients	Eudragit beads formulation code						
	F8	F9	F10	F11	F12	F13	F14
Drug (mg)	10	10	10	10	10	10	10
Eudragit S 100 (mg)	200	200	200	200	200	200	200
Sodium alginate (%)	6	4	4	4	6	6	4
Calcium chloride (%)	2	1	2	1	1	2	2
Olive oil (ml)	1	0.5	0.5	1	1	0.5	1

Table no.5: Physical Appearance, Morphological Analysis, Size Analysis and Buoyancy

Formulation code	Physical appearance	Average size (mm)± SD	Bouyancy	Floating time
F1	Round	1.543±0.079	Floating	-
F2	Oval	1.522±0.107	Non-floating	6hr
F3	Round	1.534±0.107	Floating	7hr
F4	Oval	1.440±0.104	Floating	7hr
F5	Oval	1.452±0.109	Non-floating	6.5hr
F6	Round	1.572±0.076	Floating	-
F7	Round	1.557±0.122	Floating	-
F8	Round	1.566±0.102	Floating	-
F9	Oval	1.33±0.102	Floating	4hr
F10	Oval	1.43±0.107	Non-floating	6hr
F11	Oval	1.51±0.102	Floating	7hr
F12	Oval	1.32±0.103	Floating	6hr
F13	Oval	1.40±0.104	Non-floating	6hr
F14	Oval	1.43±1.102	Floating	7hr

Table no.6: % Yield, % Drug entrapment, Drug content uniformity and Bead Water Uptake

Formulation code	% Yeild	% Drug entrapment	Mean drug content uniformity	Weight gain ratio at equilibrium Y ± SD
F1	94.23	85.6	92.37 ±0.25	0.284±0.00244
F7	96.44	95.2	85.79± 0.56	0.615±0.000551
F8	98.24	98.4	96.75± 0.25	0.6423±0.0007

Table no.7: Release kinetics of Sitagliptin microbeads

Formulation code	Zero order		First order		Higuchi model		Peppas model			Hixson model	
	r^2	K_0	r^2	K_0	r^2	K_H	r^2	K_P	N	r^2	K_S
F1	0.909	0.301	0.811	0.004	0.686	4.047	0.947	0.033	1.41	0.846	0.001
F7	0.881	0.259	0.778	0.003	0.626	3.42	0.984	0.003	1.85	0.810	0.001
F8	0.888	0.289	0.778	0.004	0.659	4.053	0.934	0.022	1.46	0.816	0.001

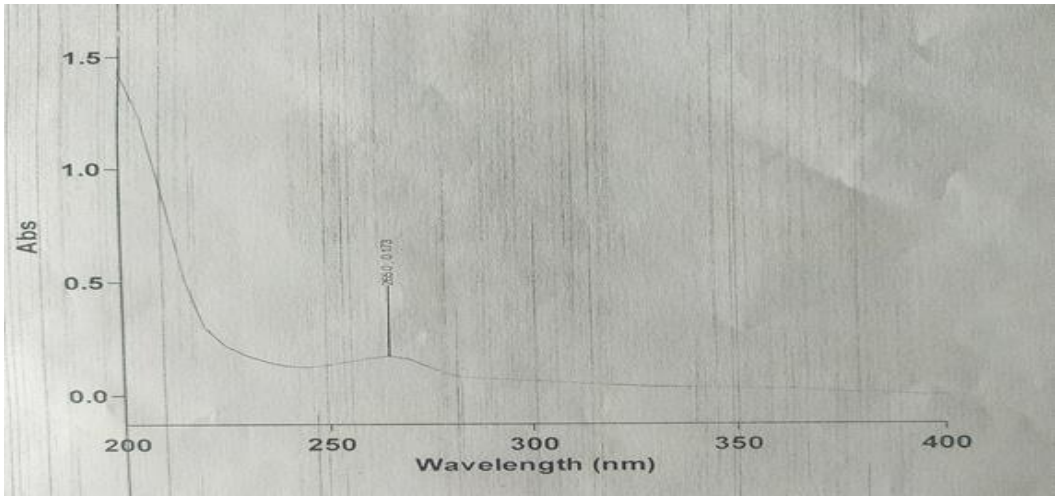

Figure1: λ max of Sitagliptin phosphate in water

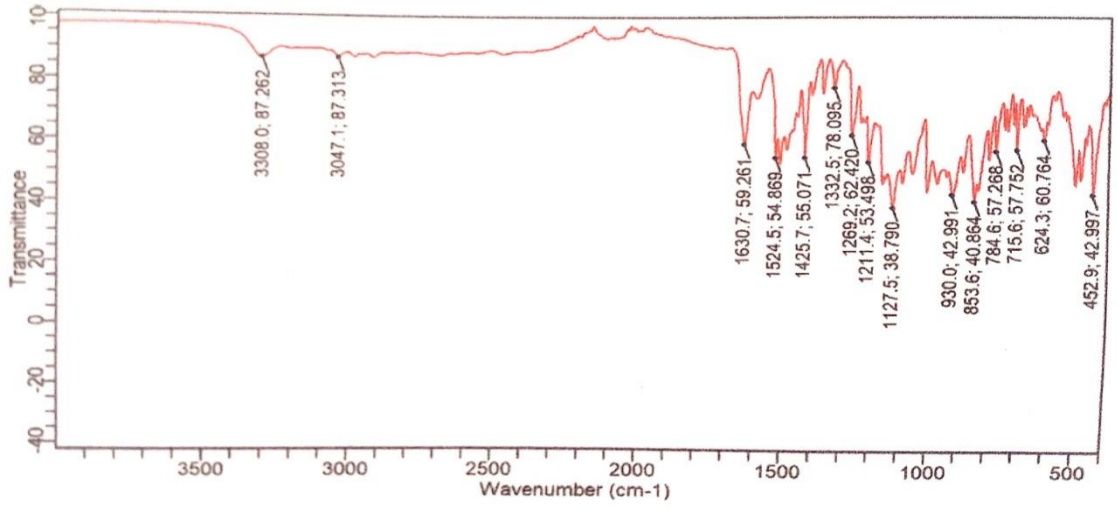

Figure 2: FT-IR of Sitagliptin phosphate

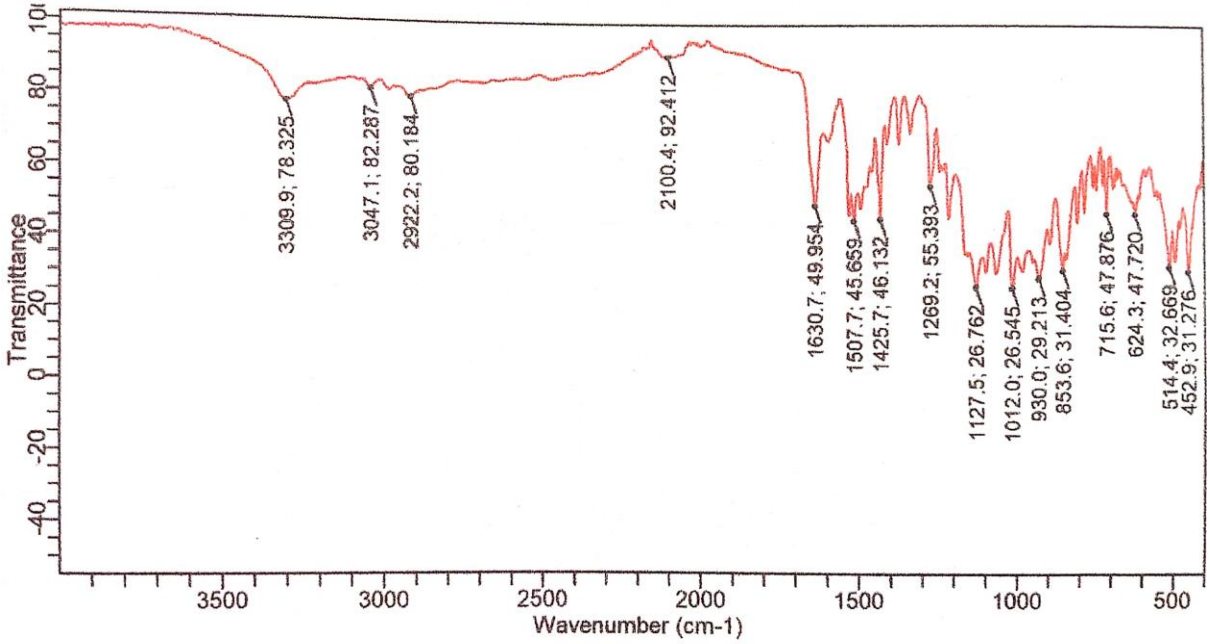

Figure 3: FT-IR of Sitagliptin phosphate with Eudragit

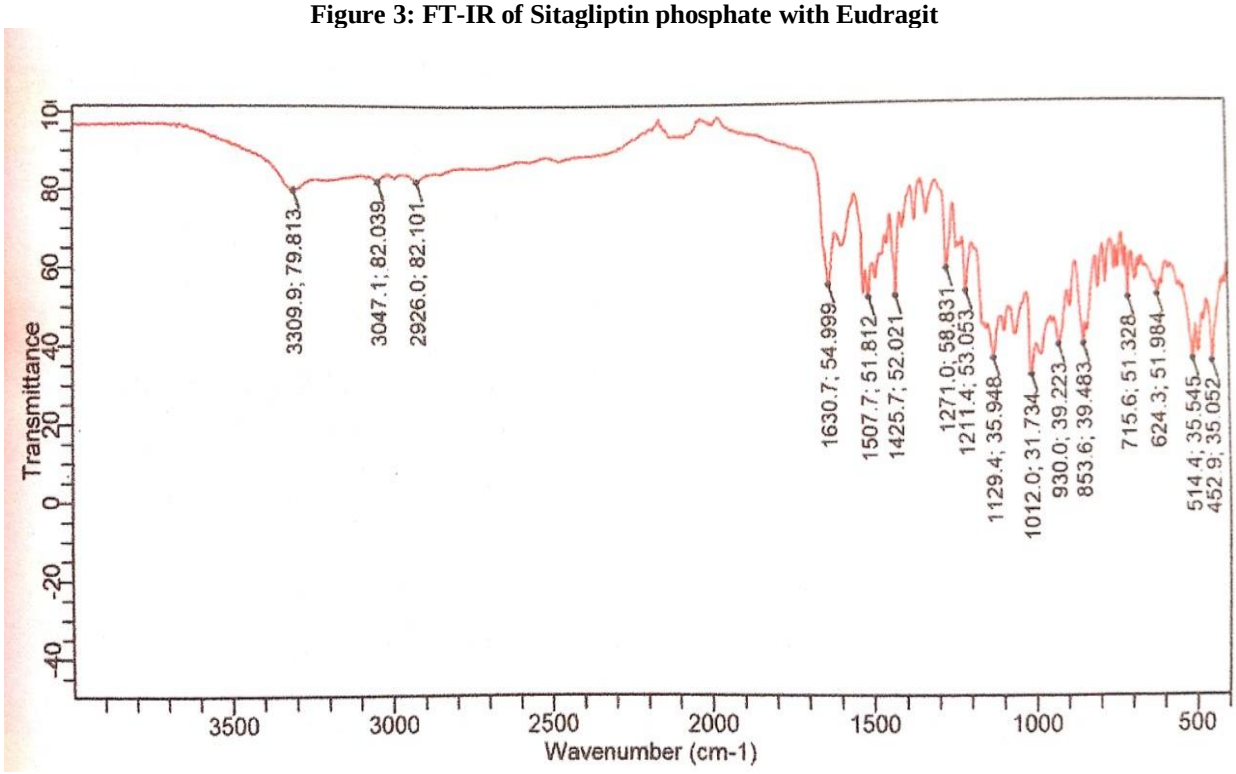

Figure 4: FT-IR of Sitagliptin phosphate with Sodium alginate

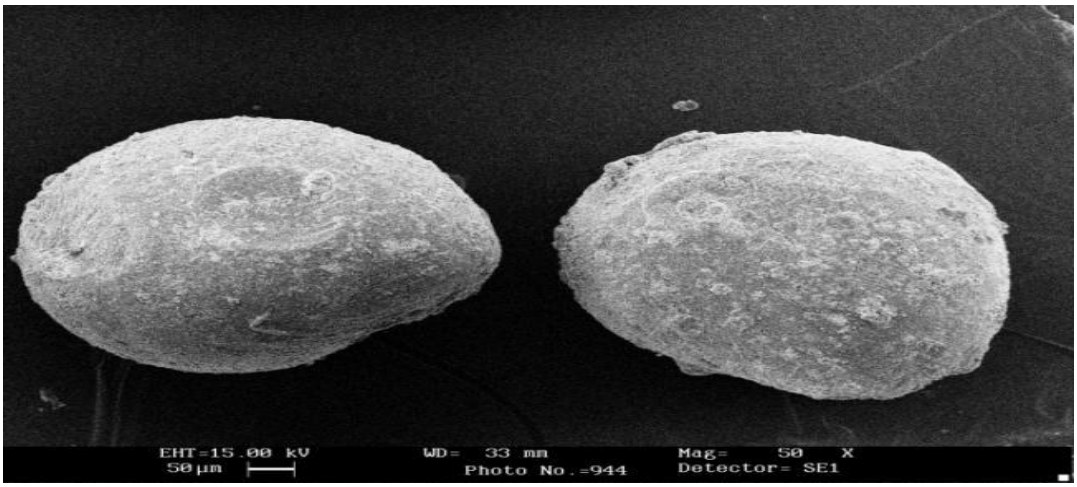

Figure 5: SEM image of HPMC bead

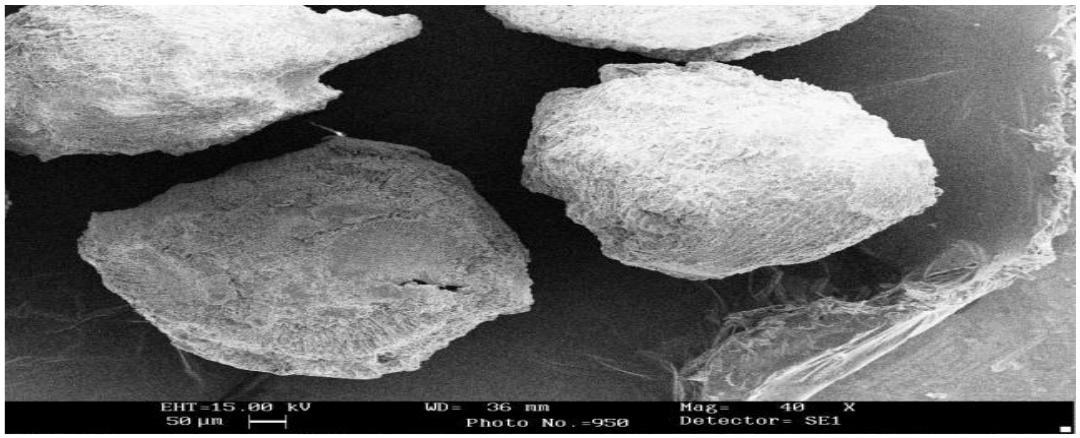

Figure 6: SEM image of Eudragit bead

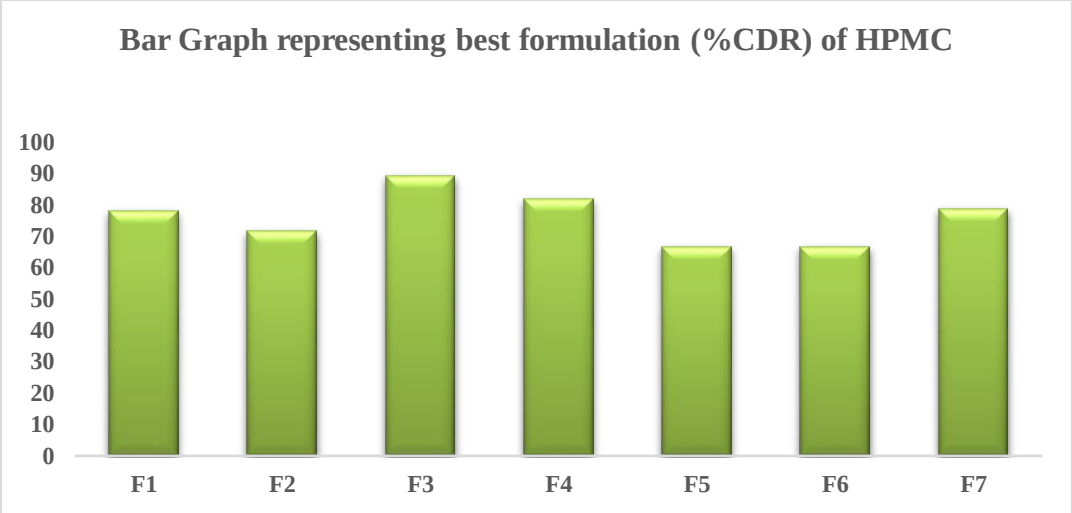

Figure 7: Bar graph of %CDR of HPMC bead

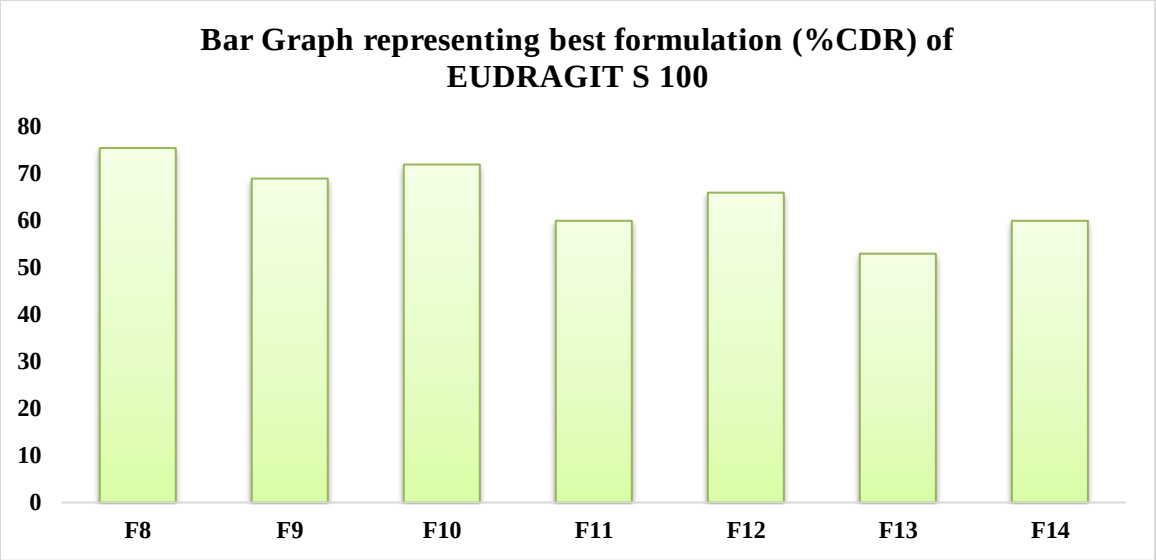

Figure 8: Bar graph of %CDR of Eudragit bead

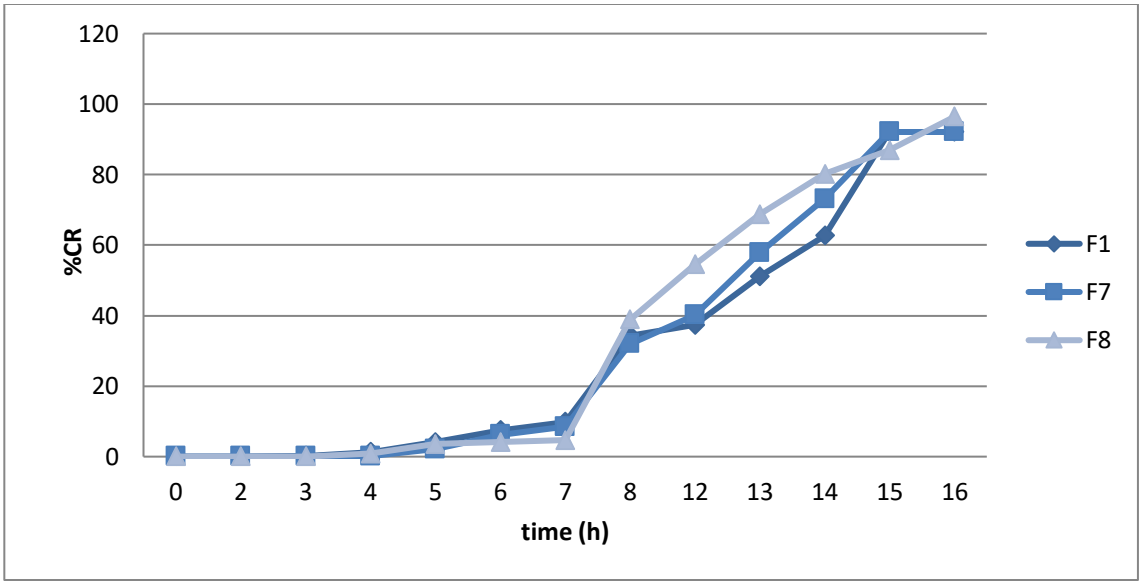

Figure 9: %CR graph of best three formulations i.e. F1, F7 and F8

***In Vitro* Drug Release Studies**

Drug release pattern in Batch 1 (different HPMC formulations F_1-F_7) was in F_3>F_4>F_7>F_1>F_2>F_5>F_6. In 5 h there was 92.091percentage drug release and 51.293percentage in 3.5 h from F_3 formulation. (Figure.7). Drug release pattern in Batch 2 (different Eudragit S 100 formulations F_8-F_{14}) was in F_8>F_{10}>F_9>F_{12}>F_{11}>F_{14}>F_{13}. In 5.5 h there was 96.414percentage drug release and 51.091percentage in 3 h from F_{14} formulation. (Figure .8).

Drug release kinetic data analysis

Kinetic study of drug release is often useful in obtaining one or two physically meaningful Parameters which are employed for comparative purposes and relating the release parameter. Moreover, a kinetic parameter can be used to study the influence of formulation factors on the drug release for statistical optimization. The drug release kinetics was studied by plotting the data obtained from the in-vitro drug release in various kinetic models. To establish the mechanism involved in drug release from the Microspheres, data of percentage drug release versus log time were plotted according to Korsmeyer–Peppas equation as drug release exponent 'n' indicates the mechanism of drug release calculated through the slope of the straight line was found to be 'n' value more than 1. If the exponent n=

0.45, then the drug release follows the Fickian diffusion and if 0.45< n < 0.85 then it is said to be non-Fickian or anomalous release. The mechanism of release for the above formulations was determined by finding the R^2 value for each kinetic model viz. zero-order, first-order, Higuchi, and Korsmeyer–Peppas corresponding to the release data of each formulation. From most of the formulations the R^2 value of Korsmeyer–Peppas model is very near to one than the R 2 values of other kinetic models. Thus, it can be said that the drug release follows Korsmeyer–Peppas model mechanism, out of which the R^2 value found to be 0.947, 0.984 and 0.934 of formulation F1, F7 and F8 respectively ,were found best amongst other formulations and 'n' value was found to be <1 hence it can be postulated that formulations F1, F7 and F8 followed non-Fickian or anomalous release. The results are shown in Table no.7.

CONCLUSION:

Sitagliptin phosphate is an insulin-sensitizing anti-diabetic drug. It was chosen as a model drug since it has a half-life (8-14 h) and bioavailability 87%. It belongs to BCS Class III drug (high solubility and low permeability). Low permeability leads to potential problem of poor bioavailability and bioequivalence of drug dosage form. Furthermore, micronized sitagliptin phosphate has shown better absorption than nonmicronized form. Hence, the absorption of drug can be enhanced using floating micro beads technique.Microbeads have been widely accepted as a means to achieve sustained release drug delivery system. The micro beads requires a polymeric substance as a carrier and a core material. Among the various methods developed for formulation of micro beads, the non-aqueous solvent evaporation method has gained much attention due to its ease of fabrication without compromising the activity of drug.HPMC is a non-ionic, swellable polymer. Hydrophilic polymer gel matrix systems are widely used in sustained drug delivery to obtain a desirable drug release profile and cost effectiveness because of their flexibility. The hydration rate of HPMC increases with increase in the hydroxyl propyl content.The present study concluded that formulation F-1, F-7 and F-8 maintained a sustained drug concentration in serum for longer period of time, which may result in enhanced absorption and thereby improved bioavailability.

REFERENCES:

1. Joseph P, Loyd V, Allen and Remington: The science and practice of pharmacy, lippincott williams and wilkins, 2013; 22(1): 759-04.
2. Michael E, Aulton, Kevin MG and Taylor: Aulton's pharmaceutics, the design and manufacture of medicines.International Elsevier Publication, 2013; 4: 465-50
3. Cong true Huynth, Doo Sung Lee, Controlled Release, Encyclopaedia of Polymeric Nanomaterial 2014; 10: 100-07.
4. Da SP, Diniz MM and De Jong G: Chitosan-alginate beads as encapsulating agents for Yarrowia lipolytica lipase: Morphological, physico-chemical and kinetic characteristics. Int J of Biol Macro 2019; 139: 621-30.
5. Kota RK and Gande S: Development and characterization of alginatemicrospheres containing olmesartan by ionotropic gelation method. International Journal of Pharmaceutical Sciences and Drug Research 2018; 10(4): 335-41.
6. Bilal M, Rasheed T, Iqbal HMN, Li C, Hu H and Zhang X: Development of silver nanoparticles loaded chitosanalginate constructs with biomedical potentialities. International Journal of Biological Macromolecules 2017; 105(1): 393-400.
7. Zakaria L, Wong TW and Anuar NK: Enhancing sustained drug release property of chitosan in spheroids through crosslinking reaction and coacervation. Powder Technology 2019; 354: 815-21.
8. Dhas P: Mechanism of drug release, In Slide Share net. Health and Medicine 2018; 1-15.
9. Bidyut Das and Juti Rani Devi: Microparticulate drug delivery system- a review. WJPLS 2016; 2(6): 243-58.
10. Giri TK: Alginate containing nano architectonics for improved cancer therapy. NASDDT 2016; 20: 565-88.
11. Victor Badron and Pavel Gurikov: A continuousapproach to the emulsion gelation method for the production of aerogel microparticle. CSPEA 2019; 566: 58-69.