J Young Pharm, 2020; 12(2) Suppl: s32-s38
A multifaceted peer reviewed journal in the field of Pharmacy
www.jyoungpharm.org | www.phcog.net

Original Article

Formulation and Evaluation of Floating Polymeric Nanoparticles of Linagliptin in Capsules

D. Prasanthi*, J. Krishna Kumari, S. Hymavathi
Department of Pharmaceutics, G. Pulla Reddy College of Pharmacy, Mehdipatnam, Hyderabad, Telangana, INDIA.

ABSTRACT

Objectives: Linagliptin is a BCS class III drug used in treatment of diabetes. In the present study floating polymeric nanoparticles of linagliptin are formulated to increase the residence time of drug in stomach by controlling drug delivery over a prolonged period of time and to increase permeability by nanosized particles, there by bioavailability can be increased. **Methods:** Polymeric nanoparticles were prepared by desolvation and ion gelation method. The prepared polymeric nanoparticles were evaluated for entrapment efficiency, drug content, percentage yield, diffusion studies and dissolution studies. **Results:** Among various formulations, GF2 formulation by ion gelation method, CF5 by desolvation (continuous addition) method and IF1 by desolation (intermittent addition) method have shown % drug release of 91.8±0.50%, 92.8±0.33% and 91.5±31% in 210min respectively. GF2 was considered as the optimized formulation based on its high entrapment efficiency of 88.6±1.09%, cumulative amount permeated of 997.0±2.15µg/cm^2 for 4hrs, Zeta potential (-20.3mV), particle size (396 nm) and SEM (spherical and smooth surface). The GF2 formulation was converted into floating drug delivery system with sodium bicarbonate and different concentration of ethyl cellulose, HPMC E15M. GF2 (1:2 ratio of drug:ethyl cellulose) was optimized as it showed prolonged drug release by retaining drug through mucosa of goat with % drug release (53.1±0.50 % at 5.5 hrs) in comparison with pure drug (99.8±0.19% at 1 hr) and it was stable as per ICH guidelines. **Conclusion:** Hence the drug release has been retarded, permeation has been enhanced and residence time of drug in the stomach has been extended by floating polymeric nanoparticles.

Key words: Floating Drug Delivery, Nanoparticles, Polymeric Nanoparticles, Desolvation Method, Ion Gelation Method, Linagliptin.

Correspondence

Dr. D. Prasanthi,

Associate Professor, G. Pulla Reddy College of Pharmacy, Mehdipatnam, Hyderabad-500028, Telangana, INDIA.

Phone: +91 9490052147

Email: prasanthidhanu@gmail.com

DOI: 10.5530/jyp.2020.12s.43

INTRODUCTION

Nanoparticles are defined as particulate dispersions or solid particles having size within the range of 10-1000nm. The drug is dissolved, attached, encapsulated or entrapped, into the nanoparticle's matrix.[1] Polymeric nanoparticles (PNPs) are prepared from a synthetic or semi synthetic polymeric block to increase the circulation half-life and to reduce phagocytic uptake and inactivation of the therapeutic moiety and can be used to deliver and target therapeutic agents.[2] They are formulated by incorporating biodegradable polymers in order to maximize tissue compatibility and minimize cytotoxicity. It has been reported that higher entrapment efficiency in PNPs can be achieved by incorporation of drug during their preparation rather than adsorption on preformed nanoparticles.[2,3] Drug release takes place in polymeric nanoparticles through their simultaneous biodegradation, followed by desorption, diffusion, or erosion. The major goals in designing nanoparticles as a delivery system are to control particle size, surface properties and release of pharmacologically active agents in order to achieve the site-specific action of the drug at the therapeutically optimal rate and dose regimen.[1-3] Chitosan is a natural polymer obtained by deactivation of chitin. It is biologically safe, non-toxic, biocompatible and biodegradable polysaccharide. Chitosan nanoparticles are formed based on electrostatic interaction between amine group of chitosan and negatively charge group of polyanion such as tripolyphosphate by ion gelation method.[4] In Desolvation method the protein or polysaccharide in aqueous phase are often desolvated by pH change or change in temperature by adding appropriate amount of counter ions.[4,5] It contains three steps: protein dissolution, protein aggregation and protein deaggregation. With the acceptable levels of desolvation and resolvation, the aggregate size might be maintained and eventually the mixtures of nanoparticles are cross linked using glutaraldehyde. The process of removing/replacing solvating water molecules, by a non-solvent, from the hydration shell of a macromolecule is named desolvation.[4,6]

Linagliptin is a BCS class III (high solubility and low permeability) drug used in treatment of diabetes. Though it has high solubility and half-life of 12hrs, bioavailability is only 30%, due to its low permeability.[7,8] In the present study floating polymeric nanoparticles of linagliptin were aimed as a novel approach to increase the residence time of drug in stomach by controlling drug delivery over a prolonged period of time and to increase permeability by nanosized particles, there by bioavailability can be increased. Nanoparticles are prepared by (ion gelation and desolvation methods) with ethyl cellulose, chitosan and gelatin as polymers. These are further converted into floating drug delivery with sodium bicarbonate and prolonging drug delivery using hydrophobic polymers like ethyl cellulose.

MATERIALS AND METHODS

Materials

Linagliptin was procured from Dr. Reddy's laboratories Ltd. Chitosan, Gelatin, sodium tri poly phosphate (STPP), glutaraldehyde, sodium bicarbonate, acetone, were procured from SD fine chemicals limited. Ethyl cellulose and HPMC E15M were procured from Yarrow Chem. Products.

Preparation

Ion Gelation Method

The polymeric nanoparticles were prepared by Ion Gelation method, chitosan was soaked in 10ml of 1%v/v glacial acetic acid. To this mixture at 700rpm, 3ml of sodium tri poly phosphate (STPP) was added drop wise and continued stirring for 30 minutes to form a nanosuspension containing nanoparticles. Nanoparticles were filtered through Whatman's filter paper, washed and dried.[9] 100mg of drug (linagliptin) was added to chitosan solution before addition of STPP. Drug: polymer ratio ranged from 1:0.25 to 1:1.25, which were coded as GF1 (1:0.25); GF2 (1:0.5); GF3 (1:0.75); GF4 (1:1) and GF5 (1:1.25) respectively.

Desolvation method

The polymeric nanoparticles were prepared by Desolvation method using gelatin as polymer. To 10ml of gelatin solution acetone was added either continuously (1ml/min) or intermittently (1ml for every 5min) at 700rpm to form turbid solution. To this nanosuspension few ml of 25%v/v glutaraldehyde was added with continuous stirring for 12hrs. Then the solvent was removed in rotary flash vacuum evaporator and nanoparticles obtained were kept for air drying.[10,11] Linagliptin was added to gelatin solution. Linagliptin: gelatin ratio ranged from 1:0.25 to 1:2, which were coded as CF1 (1:0.25); CF2 (1:0.5); CF3 (1:0.75); CF4 (1:1); CF5(1:1.25); CF6(1:1.5); CF7(1:1.75); and CF8 (1:2) respectively for continuous addition of acetone and as IF1 (1:0.25); IF2 (1:0.5); IF3 (1:0.75); IF4 (1:1); IF5(1:1.25); ICF6(1:1.5); IF7(1:1.75); and IF8 (1:2) respectively for intermittent addition of acetone.

Preparation of floating polymeric nanoparticles of linagliptin

optimized polymeric nanoparticles (GF2 formulation by ion gelation method) were converted to floating by addition of 10% of sodium bicarbonate and different concentrations of ethyl cellulose and HPMC E 15M as polymers which were filled into size '5' capsules. Quantities taken are given in Table 1.

Table 1: Preparation of floating polymeric nanoparticles of linagliptin.

Ingredients	GF2(1:0.5)	GF2(1:1)	GF2(1:1.5)	GF2(1:2)	GF2(1:2)EH
Polymeric nanoparticles (mg)	Equivalent amount of drug dose(7.5)	Equivalent amount of drug dose(7.5)	Equivalent amount of drug dose(7.5)	Equivalent amount of drug dose(7.5)	Equivalent amount of drug dose(7.5)
Ethyl cellulose (mg)	3.75	7.5	11.25	15	7.5
HPMC E 15M (mg)	-	-	-	-	7.5
Total weight(mg)	12.37	16.5	20.62	24.75	24.75

Note: Where, GF2 (1:0.5) = formulation with 1% GF2 and 0.5% ethyl cellulose as polymer;

GF2 (1:1) = formulation with 1% GF2 and 1% ethyl cellulose as polymer;

GF2 (1:1.5) = formulation with 1% GF2 and1.5% ethyl cellulose as polymer;

GF2 (1:2) = formulation with 1% GF2 and 2% ethyl cellulose as polymer;

GF2 (1:2) EH= formulation with 1% GF2 and 2% ethyl cellulose and HPMC E 15 M (in1:1) as polymer;

1% GF2 = equivalent amount of drug dose;

Drug-excipient compatibility was studied by FTIR and DSC

The spectrum analysis of pure drug and physical mixture of drug with different polymers (chitosan and gelatin) which are used for preparation of nanoparticles was studied by FTIR and DSC. FTIR spectra were recorded by preparing potassium bromide (KBr) disks using a shimadzu (Koyto, Japan) facility (model-8400S). Potassium bromide (KBr) disks were prepared by mixing few mg of sample with potassium bromide by compacting in a hydraulic press under vacuum at 6-8 tons pressure. The resultant disc was mounted in a suitable holder in IR spectrophotometer and the IR spectrum was recorded from 4000cm to 500 cm in a scan time of 12 min. The resultant spectrum was compared for any spectra changes. They were observed for the presence of characteristic peaks for the respective function functional group.[12]

DSC (differential scanning calorimetry) analysis was performed by using Q-1000 TA Instruments, USA. The instrument was calibrated with indium standard. Accurately 3-5 mg samples were weighed and placed in a closed, hermetic sample pans with pin hole. Thermo grams were obtained by heating the sample at a constant rate 10°C/min. A dry purge of nitrogen gas (50ml/min) was used for all runs. Samples were heated from 0°C to 350°C. The melting point, heat of fusion, disappearance of the crystalline sharp peak of the drug and appearance of any new peak and peak shape were noted.[12]

Evaluation of polymeric nanoparticles and floating polymeric nanoparticles

Percentage yield

The prepared drug loaded polymeric nanoparticles were collected and weighed. The weight obtained is noted as practical yield. The percentage yield was calculated by following formula.[13]

$$\% \text{ yield} = \frac{\text{Practical yield}}{\text{Theoretical yield}} \text{ X } 100$$

Determination of Drug content

Polymeric nanoparticles equivalent to 5mg of drug were dissolved in methanol and kept for stirring at 600 rpm for 3 hours respectively. The amount of the drug present in the supernatant was determined spectrophotometrically.[14]

Drug Entrapment Efficiency

Polymeric nanoparticles equivalent to 5mg of drug were taken in 2ml of distilled water and separated from the aqueous medium by ultracentrifugation at 10,000 rpm for 30 min at 5°C. Then the resulting supernatant solution was decanted and dispersed into 0.1NHCL. The amount of drug entrapped in the nanoparticles was determined as the difference between the total amount of drug used to prepare the nanoparticles and the amount of drug present in the aqueous medium.[15] The determination of entrapment efficiency was repeated three times per sample. The percentage drug entrapment was calculated using the following equation:

$$\% \text{ Drug entrapment} = \frac{\text{Amount of entrapped drug recovered}}{\text{Total amount of drug}} \times 100$$

The polymeric nanoparticles of linagliptin and floating polymeric nanoparticles were filled in size '5' capsules with drug equivalent amount and evaluated for following parameters,

Weight variation

Twenty capsules were selected at random and were weighed collectively and individually. From the collective weight, average weight was calculated. The % weight variation is calculated.

Content Uniformity

Twenty capsules were randomly selected from each batch of the prepared polymeric nanoparticles of linagliptin filled in capsules and their contents were removed and powdered. From this sample, powder (equivalent to drug dose) is accurately transferred in to 10ml volumetric flask. The volume is made up with methanol and sonicated for 30 min. Then, 1ml of the above solution is transferred in to 10ml volumetric flask and the volume is made up to the mark with 0.1N HCl. The solution is filtered through whatman filter paper and suitably diluted and the drug content was estimated spectrophotometrically by measuring absorbance at 238nm.

Zeta potential and particle size

The particle size and zeta potential were measured by photon correlation spectroscopy (Delsa Nano, Beckman Coulter Inc. UK).[16]

SEM

Scanning electron microscopy (SEM) was used to characterize the surface morphology of the prepared nanoparticles. Nanoparticle suspension was mounted on a clear-glass stub, air-dried, gold coated with Polaron E5100 sputter coater (Polaron, United Kingdom) and visualized under scanning electron microscope (Jeol 5400, Japan).[17,18]

Floating time

In this test the capsule filled with drug equivalent amount of linagliptin loaded floating polymeric nanoparticles is introduced into a 100ml beaker containing 0.1N HCl and the total duration of time for which dosage form remain floating is called floating time.[19]

In-vitro drug diffusion studies

Diffusion studies were performed using Franz diffusion cell with dialysis membrane. The cell was locally fabricated and therefore the volume of receptor compartment was 25 ml. The dialysis membrane used for diffusion studies was placed between donor and receptor compartment. Drug equivalent polymeric nanoparticles was placed on membrane and clamped together. The receptor compartment was filled with 0.1 N HCl and maintained by continuous stirring at 400 rpm with a magnetic bead and maintained at 37°C. At predetermined time intervals, 1ml samples were withdrawn and replaced with an equal volume of buffer. The samples were analysed after appropriate dilution at λmax of 238nm using spectrophotometer. From this cumulative amount permeated was calculated and plotted against function of time to study the pattern of drug permeated.[13]

In-vitro drug Dissolution studies

Dissolution studies were performed through dissolution apparatus using USP type-I (basket type) apparatus. The release of Linagliptin from the polymeric nanoparticles was studied using 0.1 N HCl in a dissolution apparatus with a rotating basket stirrer at a stirring speed of 50 rpm and a temperature of 37 ± 1°C. Drug equivalent amount of nanoparticles filled in size '5' capsules were used in each test and these were placed within each basket. Samples were withdrawn at different time intervals and replaced with 5ml of fresh dissolution medium. The withdrawn samples were assayed at 238 nm for linagliptin content using a UV visible spectrophotometer.[16]

Ex-vivo permeability studies

Ex-vivo permeability studies were carried out for optimized formulations (i.e. GF2 (1:2), GF2 formulations). Fresh intestinal tissue was removed from gastro intestinal tract (GIT) of goat obtained from local slaughter house. It was stored in saline water at frozen condition. The intestinal tissues were filled with formulations, tied to paddle by making them as pouch and the dissolution studies were carried out same as above procedure using 0.1 N HCl as medium. From this, % drug permeated was calculated and was plotted against the function of time to study the pattern of the drug release.[19]

In-vitro drug release kinetics

To study the mechanism and release kinetics, *in-vitro* release data were fitted with Zero order, First order, Higuchi release and Korsemeyer-Peppas mathematical models.[12]

Stability study

Optimized formulation i.e. GF2 (1:2) formulation was tested for stability in ambered colored bottle containers. It was stored at accelerated stability conditions (40°C ± 2°C /75% ± 5%RH) as per ICH guidelines over a period of 1month in a humidity chamber and in between the capsules were evaluated for drug content and *in-vitro* drug release every week.[12]

RESULTS

Polymeric nanoparticles were prepared using gelatin and chitosan polymers. And floating polymeric nanoparticles were prepared using ethyl cellulose and HPMC E15M. Drug-excipient compatibility with all polymers was studied by FTIR and DSC. The spectra of pure drug and optimized formulation GF2 (1:2) is given in Figure 1, which shows characteristic peaks at 1400, 1540, 1780cm^{-1} representing C-N(stretching),

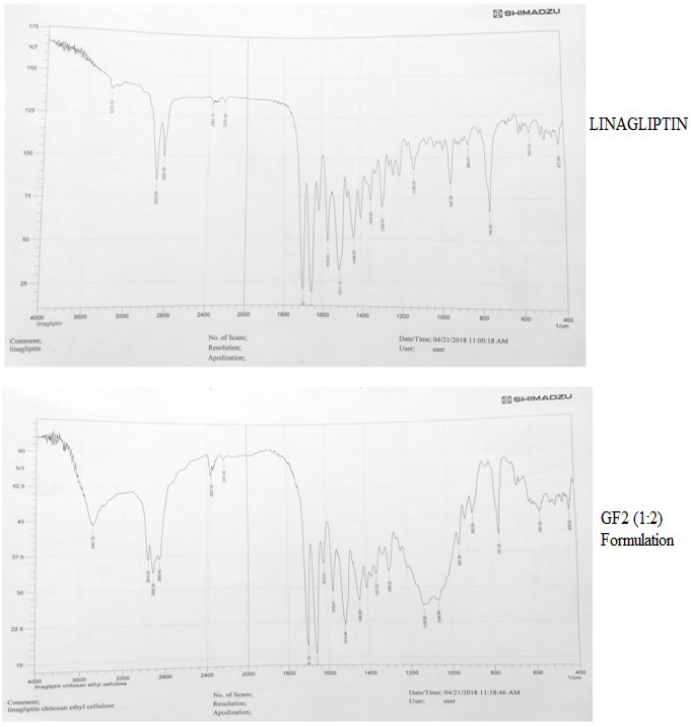

Figure 1: FTIR spectra of linagliptin and optimized floating polymeric nanoparticles formulation.

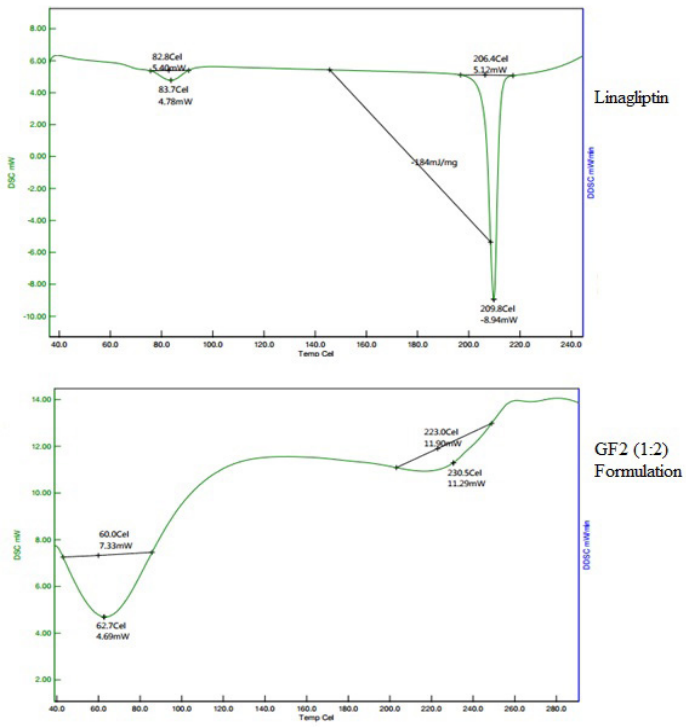

Figure 2: DSC scan of linagliptin and optimized floating polymeric nanoparticles formulation.

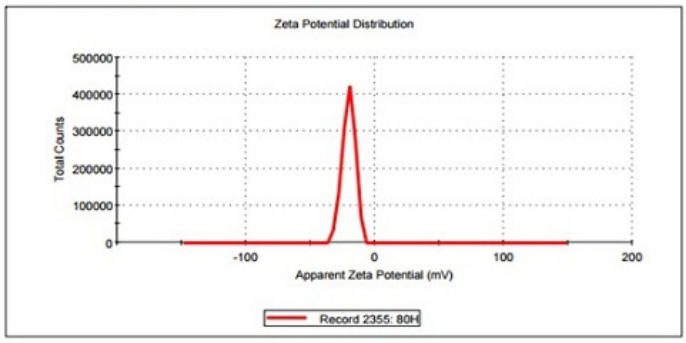

Figure 3: Zeta potential of GF2 formulation.

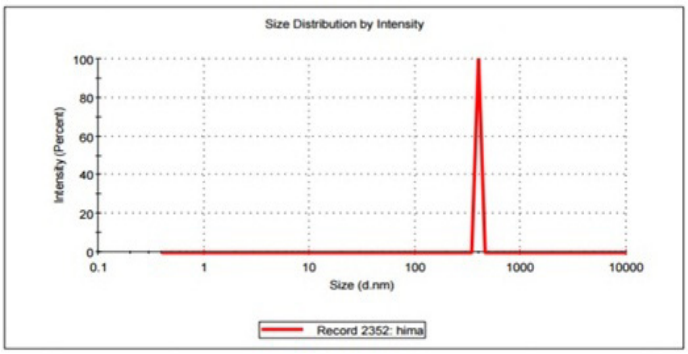

Figure 4: Particle size of GF2 formulation.

Table 2: Evaluation parameters of polymeric nanoparticles.

Formulation Code	Percentage yield (%)	Drug content (%)	Entrapment efficiency (%)	Weight variation (mg)	Content uniformity (%)
GF1	99.2±0.23	93.8±0.12	80.6±1.23	88.3±1.32	91.4±0.09
GF2	100±0.46	98.09±0.12	88.6±1.09	89.5±2.08	98.9±0.24
GF3	100±0.49	75.7±0.08	74.0±0.75	90.7±2.08	96.8±0.24
GF4	100±0.27	74.1±0.46	73.0±0.81	92.5±2.52	97.3±0.17
GF5	100±0.66	72.3±0.78	71.6±0.43	93.3±3.05	93.1±0.50
CF1	100±0.17	87.6±0.24	69.3±0.26	88.2±2.49	97.4±0.33
CF2	90.6±0.50	71.9±0.33	68.8±0.26	88.9±4.12	95.2±0.46
CF3	84.0±0.34	82.8±0.33	52.5±0.45	89.2±3.27	92.4±0.73
CF4	100±1.09	74.2±0.49	68.6±1.24	92.0±2.49	91.1±0.66
CF5	88.0±0.81	90.9±0.19	58.9±0.31	91.8±2.53	93.1±0.12
CF6	77.6±0.99	89.5±0.19	74.5±1.09	91.7±3.21	92.5±0.11
CF7	80.7±1.23	76.1±0.50	74.0±1.09	93.2±2.65	98.8±0.32
CF8	73.3±0.49	77.6±0.50	76.5±0.81	93.1±4.37	90.8±0.49
IF1	98.4±0.66	98.0±0.42	63.4±0.78	88.1±3.00	95.4±0.49
IF2	93.3±0.81	80.4±0.08	69.2±0.42	89.0±2.09	97.1±0.72
IF3	61.1±0.73	83.8±0.12	61.6±0.94	87.3±2.49	93.5±0.19
IF4	74.5±0.73	81.4±0.78	66.6±0.94	89.4±2.37	96.3±0.36
IF5	93.7±1.00	99.5±0.64	58.0±0.27	92.0±2.37	95.4±0.24
IF6	96.4±0.85	70.4±0.24	59.7±0.44	94.0±2.49	98.1±0.59
IF7	97.4±0.97	97.1±0.67	61.8±1.02	95.6±2.19	90.9±0.59
IF8	82.3±0.50	70.9±0.78	67.3±0.48	94.3±2.07	92.2±0.37

Values are expressed as mean ±SD, n=3.

N-H(Bending), C=O(Stretching) respectively. DSC scan of pure drug and optimized formulation GF2 is given in Figure 2. The pure linagliptin showed melting endothermic peak at 206°C, physical mixture showed endothermic peak at 223°C.

Percentage yield, drug content, entrapment efficiency, weight variation and content uniformity results of polymeric nanoparticles are given in Table 2.

Floating polymeric nanoparticles filled into capsules showed weight variation in range of 94.4±2.65mg to 107.1±2.59mg and content uniformity from 90.6±0.59% to 98.4±0.29%.

Zeta potential, particle size and SEM of optimized formulation GF2 is given in Figure 3, Figure 4 and Figure 5 respectively.

Floating time results of formulations is given in Table 3.

In-vitro drug diffusion studies of polymeric nanoparticles prepared by ion-gelation method showed cumulative amount permeation from 733.7±3.00 µg/cm^2 to 997.0±2.15 µg/cm^2 in which GF2 formulation

showed highest cumulative amount permeated of 997.0±2.15 µg/cm^2 at 240min and GF5 showed lowest cumulative amount permeated of 733.7±3.00 µg/cm^2 at 150min. In desolvation method by continuous addition, range of permeated amount was from 720.1±3.25 µg/cm^2 to 924.1±0.90 µg/cm^2. CF5 formulation showed highest cumulative amount permeated of 924.1±0.90 µg/cm^2 at 240min and CF2 formulation showed lowest cumulative amount permeated of 720.1±3.25 µg/cm^2 at 150min. In intermittent addition, 616.1±0.70 µg/cm^2 to 993.1±3.24 µg/cm^2 range of drug permeation was seen with formulations. Within these, IF1 showed highest cumulative amount permeated of 993.1±3.24 µg/cm^2 at 240min and the IF6 formulation showed lowest cumulative amount permeated of 616.1±0.70 µg/cm^2 at 120min.

Dissolution studies of polymeric nanoparticles prepared by ion gelation method showed drug release range from 91.8±0.50% to 97.4±0.12 % in 210 min, continuous addition in desolvation method showed 91.0±0.46% to 99.8±0.08% in 150 min and in intermittent addition range was from 91.5±0.31% in 210 min to 99.2±0.19 in 60 min. GF2 formulation showed the drug release of 91.8±0.50% in 210 min, CF5 of 92.8±0.33% at 210 min and IF1 of 91.5±0.31% at 210 min indicating the sustained / delayed release of drug from the formulation.

Percentage drug release of floating polymeric nanoparticles is given in Figure 6.

Ex-vivo permeability studies of optimized formulations GF2 nanoparticles, GF2 nanoparticles in capsule, GF2 (1:2) floating polymeric nanoparticles were performed in comparison with pure drug using fresh intestinal tissue of goat. The percentage drug permeated is given in Figure 7.

In-vitro drug release kinetics of optimized formulations GF2, CF5, IF1 and GF2 (1:2) are given in Table 4.

A stability study of optimized floating polymeric nanoparticles was performed for one month according to ICH guidelines. Physical appearance, drug content and percentage drug release parameters were evaluated every week.

DISCUSSION

Polymeric nanoparticles were prepared by ion gelation method and desolvation method. The wave numbers of the principal peaks of linagliptin appeared as characteristic peaks in the IR graphs of physical mixture of drug with excipient. Thermal behaviour of pure linagliptin and their physical mixture indicates no interaction between drug and excipient. Thus the excipients were found to be compatible.[12]

The prepared nanoparticles were evaluated for various physico chemical properties and IF3 formulation showed the lowest percentage yield of 61.1±0.73% while rest of the formulations are within the acceptable limits i.e., within the range of 70-100%. Drug content of all the formulations are within the acceptable limits i.e., within the range of 70-100% indicating that there is no loss of drug. Formulation GF2 showed the highest entrapment efficiency of 88.6±1.09%, formulation IF5 showed the lowest entrapment efficiency of 58.0±0.27% while rest of the formulations showed entrapment efficiency in the range of 60% to 80%. All the capsules passed the weight variation test as the average percent weight variation was within 7.5% limits as prescribed in the pharmacopoeia. GF2 (1:2) formulation showed the highest content uniformity of

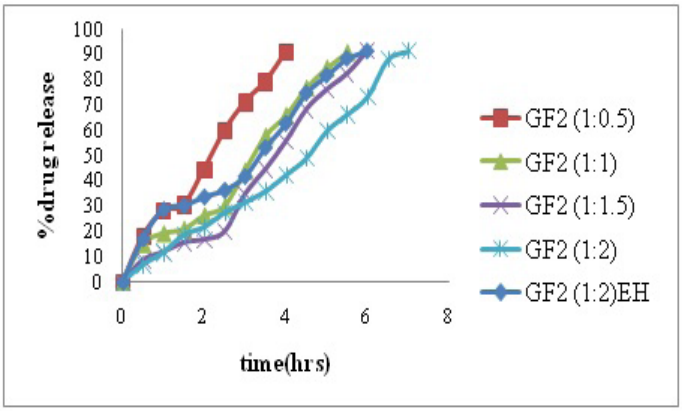

Figure 6: Percentage drug release of floating polymeric nanoparticles of linagliptin.

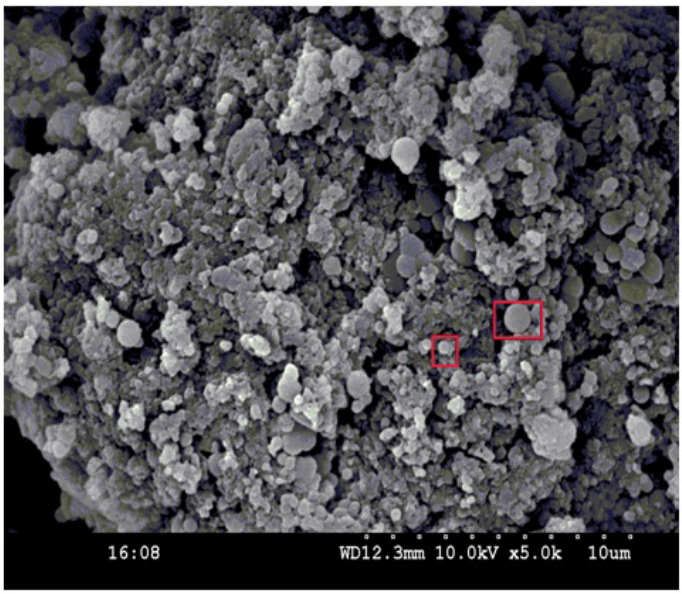

Figure 5: SEM photograph of GF2 formulation.

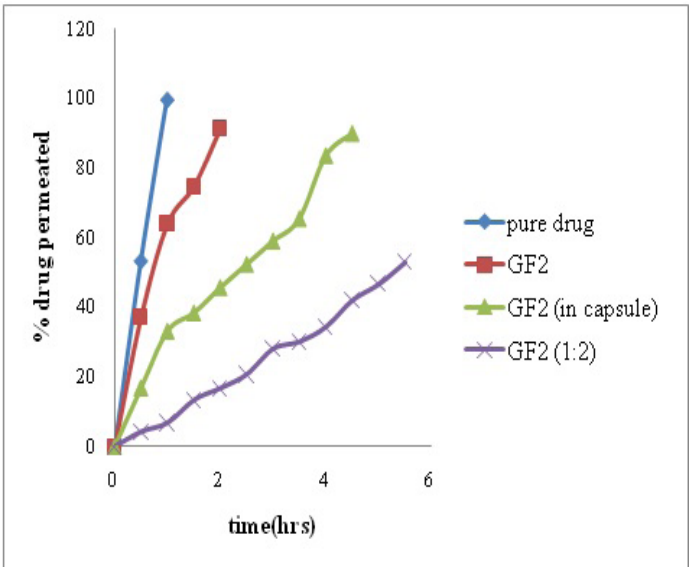

Figure 7: Percentage drug permeated in ex-vivo studies in comparison with pure drug.

Table 3: Floating time of floating polymeric nanoparticles formulations of linagliptin.

Formulation code	Floating time
GF2(1:0.5)	6hrs 47min
GF2(1:1)	7 hrs
GF2(1:1.5)	7 hrs 20min
GF2(1:2)	8 hrs
GF2(1:2)EH	7hrs 56min

98.4±0.29% and the other formulation showed the content uniformity ranging from 90.6% to 97.1%.

Zeta potential is useful in knowing the surface charge of the particle which can determine its stability.[20] Nanoparticles with a zeta potential above (±) 30 mV have been shown to be stable in suspension, as the surface charge prevents aggregation of the particles. The formulation GF2 has shown a Zeta potential of -20.3 mV. Particle size and size distribution are the most important characteristics of nanoparticle systems.[21] The particle size distribution of particles is expressed in PDI. GF2 has shown a particle size of 396 nm and PDI of 1.0 from which it can inferred that nano range has been formulated and the particle size possess large

Table 4: Drug release kinetics of optimized formulations.

Formulation code	R^2				Korsmeyer-Peppas *n*	Drug transport mechanism
	Zero	First	Higuchi	Korsmeyer-Peppas		
GF2	0.988	0.856	0.944	0.957	0.526	Anomalous transport.
CF5	0.957	0.895	0.985	0.991	0.508	Anomalous transport.
IF1	0.989	0.947	0.988	0.986	0.480	Fickian diffusion
GF2(1:2)	0.994	0.978	0.962	0.991	1.07	Super case-II transport

interfacial surface area for drug absorption. The linagliptin nanoparticles were evaluated for their surface morphology using SEM. The nanoparticles were found to be discrete, spherical with smooth surface.[22,23]

From *in vitro* drug release studies, even though GF2 formulation by ion gelation method, CF5 by desolvation (continuous addition) method and IF1 by desolvation (intermittent addition) method can be optimized based on their percent drug release of 91.8±0.50%, 92.8±0.33% and 91.5±31% in 210min respectively. GF2 was considered as the optimized formulation based on its high entrapment efficiency and cumulative amount permeated of 997.0±2.15µg/cm^2 for 240min (4hrs). Thus GF2 formulation obtained by ion gelation method was further converted into floating delivery system to increase the drug residence time by making them to float, which enhance the permeability thereby the bioavailability can be increased. GF2 (1:2) formulation showed highest floating time of 8 hrs. Since the lag time depends upon amount of sodium bicarbonate involved in carbon dioxide formation and polymer used, tough the same concentration of sodium bicarbonate (10%) was used in all formulations, floating time is varying based on the concentration of polymer used. However all formulations exhibited satisfactory floatation ability and remained floating for 6-8hrs in the dissolution medium (0.1N HCL). GF2 (1:2) showed the delayed drug release of 91.5±0.50% at 7 hrs, indicating the increase in the residence time of the drug in the stomach. The pure drug showed the permeation across the goat intestine of 99.8±0.19% at 1hr, where as GF2 (1:2) formulation showed permeation of 53.1±0.50% in 5.5 hrs by retaining the drug. Hence the increase in permeation of the drug has been achieved. It is observed from release kinetics GF2 (1:2) formulation followed zero order release kinetics with super case –II transport mechanism. The formulation was also stable for one month at accelerated stability conditions according to ICH guidelines.[12]

CONCLUSION

Floating polymeric nanoparticles of linagliptin prepared by ion gelation method using chitosan and ethyl cellulose were able to increase the residence time of drug in stomach by floating and retarding drug release, permeability of drug was enhanced by nano size of particles. Hence the objective of enhancing bioavailability is achieved.

ACKNOWLEDGEMENT

The authors would like to acknowledge G.Pulla Reddy College of Pharmacy for providing the facilites for research work.

REFERENCES

1. Mohanlal VJ, Chen Y. Nanoparticles: Review. TJPR. 2006;5(1):561-73.
2. Aarti PN, Mukesh PR, Shilpa PC. Nanoparticles: An overview. IJRD. 2014;3(5):1121-7.
3. Kuldeep M, Singh SK, Mishra DN, Birender S. Nanoparticles: An Advance Technique for Drug Delivery. RJPBCS. 2012;3(3):1186-208.
4. Abhishek G, Sharad V, Pramod KS, Nitin K. Formulation, Characterization and Application on Nanoparticle: A Review. Pelagia Research Library. 2011;2(2):17-26.
5. Adriana PHB, María TAM, Manuel ICH, Leandro JMO. Preparation of chatoyant nanoparticles modified with sodium alginate with potential for controlled drug release. Technical-scientifical Biannual Publication. 2016;12(3):75-83.
6. Archana. Formulation and Evaluation of Naproxen Sodium Loaded Bovin Serum Albumin Nanoparticles by Desolvation Technique. AJPTI. 2015;03(14):23-33.
7. Navaneetha K, Navya A, Venkateshwara B, Reddy T, Saritha NJ. Formulation and *in-vitro* evaluation of nanoparticles of linagliptin. WJPR. 2017;6(7):1319-28.
8. Prasanthi D, Yanmanagandla D, Sripada RD. Formulation and evaluation of linagliptin mucoadhesive microspheres. Int Res J Pharm. 2018;9(5):11-7.
9. Kalpana N, Shailendra KS, Dina NM. Chitosan Nanoparticles: A Promising System in Novel Drug Delivery. Chemical and Pharmaceutical Bulletin. 2010;58(11):1423-30.
10. Krishna SS. Preparation of sodium alginate nanoparticles by desolvation technique using is propyl alcohol as desolvating agent. IJAP. 2015;4 (5):2320-4923.
11. Krishna S, Chandavath V. Preparation and characterization of mefenamic acid loaded bovine serum albumin nanoparticles by desolvation technique using acetone as desolvating agent. Scholars Research Library. 2014;6(6):207-26.
12. Amoolya C, Prasanthi D. Solubility Enhancement of Aripiprazole by Solid-Self Emulsifying Drug Delivery Systems. Int J Pharm Sci Drug Res. 2018;10(4):233-45.
13. Krishna AK, Amareshwar P, Chakravarty P. Different techniques used for the preparation of nanoparticles using natural polymers and their application. Int J Pharm Pharm Sci. 2011;3(2):45-50.
14. Aenugu SR, Abba RKS. Preparation and Characterization of aspirin loaded ethyl cellulose nanoparticles by solvent evaporation technique. WJPPS. 2014;3(6):81-93.
15. Amulyaratna B, Sunit KS. Preparation and evaluation of glibenclamide-loaded biodegradable nanoparticles. TJPR. 2012;11(3):345-50.

16. Anto S, Azhagesh R, Bharathi S. Preparation, characterization and evaluation of nanoparticles containing hypolipidemic drug and antihypertensive drug. IJBA. 2011;2(3):949-53.
17. Alshamsan A. Nanoprecipitation is more efficient than emulsion solvent evaporation method to encapsulate cucurbitacin I in PLGA nanoparticles. Saudi Pharm J. 2014;22(3):219-22.
18. Patel R, Gajra B, Parikh RH, Gayatri P. Ganciclovir Loaded Chitosan Nanoparticles: Preparation and Characterization. Journal of Nanomedicine and Nanotechnology. 2016;7(6):1-8.
19. Pavan KP, Sree P. Formulation and *in vitro* evaluation of floating microspheres of dextromethorphan hydrobromide. Materials Science. 2014;6(4):1-8.
20. Sree LV, Krishna S. Formulation of Mefenamic acid loaded polymeric nanoparticles by ionotropic gelation technique for the treatment of rheumatoid arthritis. International Journal of Advances in Pharmaceutics. 2016;5(6):151-9.
21. Nagarwal RC, Kant S, Singh PN, Maiti P, Pandit JK. Polymeric nanoparticulate system. J Control Release. 2009;136(1):2-13.
22. Nagavarma BVN, Hemant KS, Yadav AA, Vasudha LS, Shiva KHG. Different techniques for preparation of polymeric nanoparticles: A review. Asian J Pharm Clin Res. 2012; 5(3): 16-23.
23. Naha A, Kiran S, Rai I, Vora B, Reddy DA, Kartika P. Preparation and evaluation of polymeric nanoparticles of glibenclamide. JDDT. 2014;4(5):190-2.

Article History: Submission Date : 09-03-2020; Revised Date : 03-05-2020; Acceptance Date : 07-06-2020.
Cite this article: Prasanthi D, Kumari JK, Hymavathi S. Formulation and Evaluation of Floating Polymeric Nanoparticles of Linagliptin in Capsules. J Young Pharm. 2020;12(2)Suppl:s32-s8.