International Journal of Pharmaceutics and Drug Research
ISSN: 2347-6346
Available online at http://ijpdr.com

Original Research Article

PREPARATION, OPTIMIZATION AND CHARACTERIZATION OF NATEGLINIDE CONTAINING MICROSPHERES IN DIABETES

[1]Sudesh Kushwaha*,[2] Shubham Patel, [2]Gajendra Sen, [2]Jyoti Sen, [2]Abhishek Rawat, [1]Yuvraj Singh Dangi, [2] Shailendra Patil

[1]Sagar Institute of Pharmaceutical Sciences, Sagar M.P. (470228)

[2]SVN Institute of Pharmaceutical Sciences, Swami Vivekanand University, Sagar M.P. (470228)

***Correspondence Info:**
Sudesh Kushwaha
Sagar Institute of Pharmaceutical Sciences, Sagar M.P. (470228)
Email:
patelswadesh30@gmail.com

***Article History:**

Received: 21/04/2024
Revised: 18/05/2024
Accepted: 27/05/2024

ABSTRACT

Gastroretentive drug delivery systems have made it possible to deliver the drugs in the stomach for prolonged period of time. Thus it is envisaged to develop a mucoadhesive microspheres based drug delivery system, which can be retained in the stomach for prolonged period of time by virtue of their mucoadhesive properties. The intimate contact of the mucoadhesive polymer with the mucous surface can result in an increased drug retention time and drug concentration in the GI tract. Nateglinide is a oral anti-diabetic drug used in Type-II diabetes (non-insulin dependent diabetes mellitus) that can acutely lower the blood glucose level in humans by stimulation the release of insulin from the pancreas. Its short biological half life (1-1.5 hours) necessitates that it be administered in 2 or 3 doses of 60 to 120 mg of per day. Moreover, the site of absorption of nateglinide is in the stomach. Thus the development of mucoadhesive controlled-release microspheres would be eliminating the entire problem associated with drug.

Key Words: Microspheres, Diabetes, Nateglinide, Gastro Retention.

INTRODUCTION

With traditional drug delivery systems, the drug level in the blood follows the in which the level rises after each administration of the drug and then decreases until the next administration. The key point with traditional drug administration is that the blood level of the agent should remain between a maximum value, which may represent a toxic level, and a minimum value, below which the drug is no longer effective. Oral delivery of drugs is by far the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in formulation, etc. many of the drug delivery systems, available in the market are oral drug delivery type systems (Streubel *et al.,* 2003).

Oral drug delivery systems have progressed from immediate release to site-specific delivery over a period of time. Every patient would always like to have an ideal drug delivery system possessing the two main properties that are single dose or less frequent dosing for the whole duration of treatment and the dosage from must release active drug directly at the site of the action. Attention has been focused particularly on orally administrated sustained drug delivery systems because of the ease of the administration via the oral route as well as the ease and economy of manufacture of oral dosage forms, sustained release describes the delivery of drug from the dosage forms over an extended period of time. It also implies delayed

therapeutic action and sustained duration of therapeutic affect. Sustained release means not only prolonged duration of drug delivery and prolonged release, but also implies predictability and reproducibility of drug release kinetics.

A number of different oral sustained drug delivery systems are based on-different modes of operation and have been variously named, for example, as a dissolution controlled systems, diffusion controlled systems, ion-exchange resins, osmotically controlled systems, erodible matrix systems, pH-independent formulations, swelling controlled systems, and the like (Klausner *et al.,* 2003). Polymers are becoming increasingly important in the field of drug delivery. The pharmaceutical applications of polymers range from their use as binders in tablets to viscosity and flow controlling agents in liquids, suspensions and emulsions. Polymers can be used as film coatings to disguise the unpleasant taste of a drug, to enhance drug stability and to modify drug release characteristics. The review focuses on the significance of pharmaceutical polymer for controlled drug delivery applications. Sixty million patients benefit from advanced drug delivery systems today, receiving safer and more effective doses of the medicines they need to fight a variety of human ailments, including cancer.

Controlled Drug Delivery (CDD) occurs when a polymer, whether natural or synthetic, is judiciously combined with a drug or other active agent in such a way that the active agent is released from the material in a predesigned manner (Deshpande *et al.,* 1997). The release of the active agent may be constant over a long period, it may be cyclic over a long period, or it may be triggered by the environment or other external events.

In any case, the purpose behind controlling the drug delivery isto achieve more effective therapies while eliminating the potential for both under and overdosing.

An orally administered controlled drug delivery system encounters a wide range of highly variable conditions, such as pH agitation intensity, and composition of the gastrointestinal fluids as it passes down the G.I tract (Jaimini *et al.,* 2007). Considerable efforts have been made to design oral controlled drug delivery systems that produce more predictable and increased bioavailability of drugs. However, the development process is precluded by several physiological difficulties, like inability to retain and localize the drug delivery system within desired regions of the G.I tract and highly variable nature of the gastric emptying process.

An important factor, which may adversely affect the performance of an oral controlled drug delivery system, is G.I transit time. The time for absorption in the GI transit in humans, estimated to be 8-10 hrs from mouth to colon, is relatively brief with considerable fluctuation. G.I transit time vary widely between individuals, and depends up on the physical properties of the object ingested and the physiological conditions of the gut. This variability may lead to predictable bioavailability and times to achieve peak plasma levels. One of the important determinants of G.I transit is the residence time in the stomach.

Majority of the drug are well absorbed from all the regions of the G.I tract while some are absorbed only from specific areas, principally due to their low permeability or solubility in the intestinal tract, their chemical instability, the binding of the drug to the gut contents, as well as to the degradation of the drug by the microorganisms present in the colon. Therefore, in instances where the drug is not absorbed uniformly over the G.I tract, the rate of drug absorption may not be constant inspite of the drug delivery system delivering the drugs at a constant rate into the G.I fluids (Innuccelli *et al.,* 1998). More particularly, in instances where a drugs has a clear cut "absorption window", i.e., the drug is absorbed only from specific region of the stomach or upper part of the small intestine, it may not completely absorbed when administered in the form of a typical oral controlled drug delivery system, it is due to the relatively brief gastric emptying in humans, which normally averages 2-3 hrs through the major absorption zone. It may cause incomplete drug release from the dosage form at absorption sites leading to diminished efficacy of the administered dose. It is apparent that for a drug having such an "absorption window", an effective oral controlled drug delivery system should be designed not only to deliver the drug at a controlled rate, but also to retain the drug in the stomach for a long period of time. For this drug, increased or more predictable availability would result if controlled release systems could be retained in the stomach for extended periods of time.

Nearly all of the currently marketed monolithic oral ER dosage forms fall into one of the following two technologies: 1. Hydrophilic, hydrophobic or inert matrix systems: These consist of a rate controlling polymer matrix through which the drug is dissolved or dispersed. 2. Reservoir (coated) systems where drugcontaining core is enclosed within a polymer coating. Depending on the polymer used, two types of reservoir systems are considered (Vyas and Khar, 2006). (a) Simple diffusion/erosion systems where a drug-containing core is enclosed within hydrophilic and/or water-insoluble polymer coatings. Drug release is achieved by diffusion of the drug through the coating or after the erosion of the polymer coating. (b) Osmotic systems where the drug core is contained within a semi-permeable polymer membrane with a mechanical/laser drilled hole for drug delivery. Drug release is achieved by osmotic pressure generated within the tablet core.

Nateglinide (USP)

Nateglinide is an oral antidiabetic agent used in the management of Type 2 diabetes mellitus [also known as non-insulin dependent diabetes mellitus (NIDDM) or adult-onset diabetes]. Nateglinide is structurally unrelated to the oral sulfonylurea insulin secretagogues. Nateglinide is an amino-acid derivative that lowers blood glucose levels by stimulating insulin secretion from the pancreas. This action is dependent upon functioning beta-cells in the pancreatic islets. Nateglinide interacts with the ATP-sensitive potassium (K+ATP) channel on pancreatic beta-cells. The subsequent depolarization of the beta cell opens the calcium channel, producing calcium influx and insulin secretion. The extent of insulin release is glucose dependent and diminishes at low glucose levels. Nateglinide is highly tissue

selective with low affinity for heart and skeletal muscle (Hanefeld *et al.,* 2000).

MATERIALS AND METHODS

Material

The drug Nateglinide was generously supplied as a gift sample from Glenmark Pharmaceutical Industries Ltd. Nasik, India. PAA was procured from Himedia Laboratories Pvt. Ltd, Mumbai, India. PVP, span 80, and n-hexane were procured from central drug house Pvt. Ltd. Mumbai, India. All other chemicals were used of analytical grade.

Preformulation Studies

1. Physical appearance: The supplied sample was a white to off white amorphous powder.

2. Melting point: The melting point of Nateglinide was found to be 129-130°C, which is accordance with the value specified in Martindale.

3. Solubility: The solubility profile of Nateglinide is determined to understand its solubility in various solvents. This involves testing a known amount of Nateglinide in different solvents, such as water, ethanol, methanol, and various buffer solutions, at different temperatures.

4. Partition coefficient: The partition coefficient (log P) of Nateglinide is measured to determine its lipophilicity, which influences the drug's absorption and distribution in the body. This is typically done using the shake-flask method, where the partitioning of Nateglinide between n-octanol and water phases is observed. A higher log P value indicates greater lipid solubility, providing insights into how the drug will behave in biological systems.

5. UV-Vis spectrophotometry: Calibration curve for Nateglinide is established to enable accurate quantification during further studies. This involves preparing a series of standard solutions at known concentrations and measuring their absorbance using an appropriate analytical method, such as UV-Vis spectrophotometry. The resulting calibration curve, which plots concentration against absorbance, should exhibit a linear relationship.

Calibration curve of Nateglinide in SIF (pH 1.2)

Disodium hydrogen orthophosphate (28.8g), potassium dihydrogen orthophosphate (11.45 g) and pancreatin (10.0 g) were mixed in about 100 ml of distilled water and the volume was made up to 1000 ml with distilled water. The pH of solution was adjusted to 1.2 with 0.1N hydrochloric acid or 0.1 N NaOH as required (Jain *et al.,* 2009).

Preparation of standard stock solution

An accurately weighed quantity of nateglinide (10 mg) was dissolved in 2 ml of methanol and volume made up to 100 ml of simulated intestinal fluid (pH 1.2) to prepare a stock solution of 100 µg/ml of drug.

Determination of absorption maxima (λ_{max})

Standard stock solution was diluted to 10 µg/ml with simulated intestinal fluid (pH 1.2), then it was scanned between 200-400 nm for the absorption maxima by UV/visible spectrophotometer (Shimadzu 1700, Japan). The absorption maxima (λ_{max}) was obtained at 210 nm as shown in Fig. 2.

Procedure

From the above stock solution, aliquots of 0.2, 0.4,… 1.8, 2.0 ml were withdrawn in a

series of 10 ml volumetric flasks and diluted to 10 ml with simulated intestinal fluid (pH 1.2). This gave solutions in a final concentration range of 2-20 µg/ml. The absorbance of each solution was measured using UV/visible spectrophotometer (Shimadzu 1700, Japan) at λ_{max} 210 nm. The data were processed using computer for the various parameters, which are reported in Table 3 and graphically shown in Fig. 2. Same procedure follows in SGF (pH 6.8) and in PBS (pH 7.4) show in Table (4 & 5).

Drug compatibility studies with selected polymers

Drug compatibility with polymers (PAA-PVP) was observed. Accurately weighed quantity (10mg) of Nateglinide placed in 10ml volumetric flask and 10 mg of each polymer (i.e., PAA and PVP) were added in flasks separately and volume was made up to 10ml with methanol. The solution of each flask was filtered and 0.1ml was transferred in 10ml volumetric flask and volume was made up to the mark with methanol. Absorbance was measured for each solution using Shimadzu UV- 1800 spectrophotometer against respective blank solution. The absorbance data are presented in Table 6.

Preparation of PAA-PVP Mucoadhesive Microspheres

The mucoadhesive microspheres were prepared by interpolymer complexation and solvent diffusion method described by Chun *et al*, (2005) with slight modification. PAA (1 g) and PVP (0.2g) was dissolved in 5 mL of ethanol/water (7/3 v/v) mixture. And then drug 40 mg was dissolved in it. The solution was sequentially dropped using a syringe, into of soya oil containing (1.5% v/v) span80 and stirred with a magnetic stirrer (Remi, India) at 500 rpm at an ambient temperature for 4 hrs. The prepared microspheres were gradually hardened and collected by filtration. They were washed three times with n-hexane and dried at room temperature.

Optimization of formulation and process variables

Various formulation and process variables i.e. polymer and drug concentration, phase volumeratio, surfactant concentration, stirring time and stirring speed which could affect the preparation and properties of microspheres were identified and studied. The optimization was done on the basis of particle size and drug loading efficiency.

Optimization of polymer (PVP-PAA) concentration

For optimization of PVP-PAA concentration, the microspheres formulations were prepared with varying concentration of PVP-PAA *i.e.* 0.1:1%, 0.2:1%, 0.3:1% and 0.4:1% w/v while keeping other parameters constant. Optimization was done on the basis of average particle size and shape. The observations are recorded and shown in Table 7 and Fig. 5.

Optimization of drug concentration

For optimization of drug concentration, the microspheres formulations were prepared with varying percentage of drug *viz.* 20:100, 40:100, 60:100, 80:100 % w/w of drug while keeping other parameters constant. Optimization was done on the basis of drug loading and particle size. The observations are

recoded and shown in Table 8 and graphically shown in Fig 6

Optimization of internal phase/external phase ratio

For optimization of internal/external phase ratio, the microspheres formulations P2D2 was selected and different microspheres formulations were prepared with ratio 1:1, 1:5 and 1:10 phase ratio while keeping the other parameters constant. The effect of phase ratio on the particle size and percentage drug loading is reported in table 9 and shown in fig. 7.

Optimization of surfactant concentration

For optimization of surfactant (span-80) concentrations, formulation P2D2I2 was selected. Keeping the other parameters constant, microspheres formulations were prepared using different surfactant concentrations in external phase (Bera *et al.,* 2014). The effect of surfactant concentration formulation is reported in Table 10 and shown in Fig 8.

Optimization of stirring speed

For the optimization of stirring speed, formulation (P2D2I2E3) was selected and microspheres were prepared by taking varying stirring speed i.e. 300, 400, 500 and 600 rpm (Remi, India) while keeping the other variables constant. The optimization was done on the basis of average particle size and maximum % drug loading. The observations are recorded and shown in Table 11 and Fig.9. On the basis of formulation and process variable studies the optimized microspheres formulation was obtained as recorded in Table 12.

Characterization of PAA-PVP microspheres

Shape and surface morphology

Scanning electron microscopy (SEM, JealJX 840-A, Tokyo, Japan) was performed to characterize the surface of formed mucoadhesive microspheres (Patel *et al.,* 2005). Samples for SEM were prepared by lightly sprinkling the powder on a double adhesive tape stuck to an aluminum stub. The stubs were then coated with gold film under reduced pressure. This film acts as a conducting medium on which a stream of electron was allowed to flow and then photograph was taken with scanning electron microscope.

Particle size and Drug Entrapment Efficiency

Microspheres were studied microscopically for their size and size distribution using calibrated ocular micrometer (Belgamwar *et al.,* 2009).

For determination drug entrapment efficiency 500mg of microspheres containing a drug were taken, crushed by trituration and suspended in a minimal amount of dichloromethane (10ml) for dissolving the coat shell of the microspheres. The suspension was suitably diluted with 0.1N HCl buffer (100mL) for 1hr and filtered to separate the shell fragments. Then Drug entrapment efficiency was analyzed after suitable dilution by spectrophotometrically with a UV-detector (Shimadzu, UV- 1800) at 210 nm. The drug entrapment efficiency was calculated as follows:

Drug entrapment efficiency = Calculated drug concentration ×100

Theoretical drug content

Degree of Swelling of Microspheres

For estimating the degree of swelling 1gm of microsphere were suspended in 5 mL of simulated gastric fluid USP (pH 1.2). The particle size was monitored by microscopy technique every 1 hour using an optical microscope (Labomed CX RIII). The increase in particle size of the microspheres was noted for up to 8 hours.

The formula used for calculation of degree of swelling is given below:

$$\alpha = [\omega_g - \omega_o]/\omega_o$$

Where α = degree of swelling,

ω_0 = initial weight of microspheres

ω_g = final weight of microspheres

***In vitro* Wash-off Test for Microspheres**

The mucoadhesive properties of the microspheres were evaluated by *in vitro* wash-off test as reported by Behera *et al*., 2008). For this 1 cm piece of rat stomach mucosa was tied onto a glass slide using thread. About 100 microspheres was spread onto the wet, rinsed, tissue specimen, and the prepared slide was hung onto the groves of a USP tablet disintegrating test apparatus. The disintegrating test apparatus was operated such that the tissue specimen was given regular up and down movements in a beaker containing the simulated gastric fluid USP (pH 1.2). At the end of 1 hr, 5 hr and 10 hr intervals and the number of microspheres still adhering onto the tissue was measured. The results of *in vitro* wash-off test of are shown in Tables 15 and Fig.12.

***In vitro* drug release studies in simulated gastrointestinal fluids of different medium**

The dissolution test of nateglinide microspheres was carried out by the paddle type-II dissolution apparatus specified in USP XXIII. 500 mg of nateglinide loaded microspheres was weighed accurately and gently spread over the surface of 900 mL of dissolution medium. The content was rotated at 100 rpm and thermostatically controlled at 37±0.5°C. Perfect sink condition was prevailed during the drug dissolution. The release was tested in dissolution medium of SGF (pH 1.2), SIF (pH 6.8) and PBS (pH 7.4). An aliquot of the release medium was withdrawn at predetermined time intervals and an equivalent amount of fresh medium was added to the release medium. The collected samples were filtered through 0.45µm-syringe filter (Millipore millex HN) and analyzed spectrophotometricaly. The observations are recorded in Table 16 and graphically shown in Fig. 13.

RESULTS AND DISCUSSION

Table 1: Solubility Profile

S. No.	Solvent (S)	Observed solubility
1	Distilled water	-
2	Ethanol (95%)	+++
3	Methanol	+++
4	Chloroform	+++
5	Octanol	++
6	Acetonotrile	++

++++ Very soluble, 1 part soluble in less than 1 part of solvent

+++ Freely soluble: 1 in 1-10 parts of solvent

++ Sparingly soluble: 1 in 30-100 parts of solvent

\+ Slightly soluble: 1 in 100-1000 parts of solvent

\- Practically insoluble: 1 part soluble in > 1000 parts of solvent

Table 2: Partition Coefficient:

S.No.	Solvent system(s)	Partition coefficient (P)
1	n-octanol / water	0.2
2	n-octanol / PBS (pH 7.4)	0.4

Table 3: Calibration Curve of Nateglinide in SIF (pH 1.2) at λ_{max} 210 nm

S. No.	Concentration (µg/ml)	Absorbance	Statistical Analysis
1.	2	0.087	Correlation Coefficient R^2= 0.99646 Straight line equation y=0.11247x + 0.00355
2.	4	0.247	
3.	6	0.359	
4.	8	0.478	
5.	10	0.555	
6.	12	0.696	
7.	14	0.782	
8.	16	0.874	
9.	18	1.006	
10.	20	1.087	

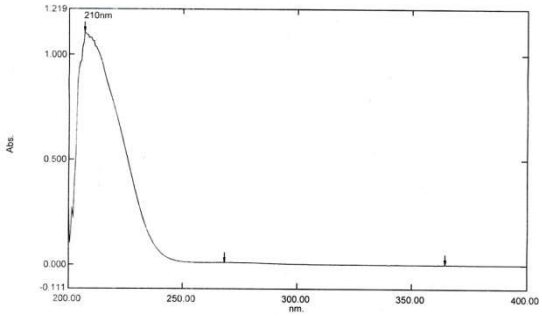


Figure 1: UV absorption scans of Nateglinide

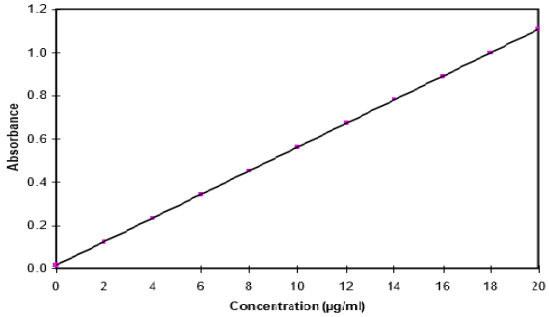


Figure 2: Calibration Curve of Nateglinide

Table 4: Calibration curve of nateglinide in SIF (pH 6.8) at λ_{max} 210 nm

S. No.	Concentration (µg/ml)	Absorbance	Statistical Analysis
1.	2	0.095	Correlation CoefficientR^2= 0.99549 Straight line equation y = 0.09678x + 0.02587
2.	4	0.203	
3.	6	0.338	
4.	8	0.405	
5.	10	0.530	
6.	12	0.645	
7.	14	0.712	
8.	16	0.785	
9.	18	0.899	
10.	20	1.000	

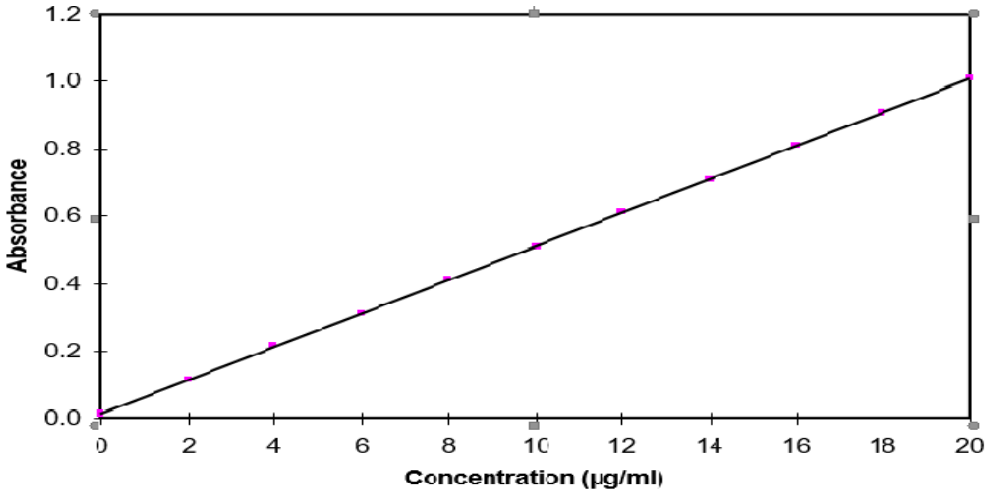


Figure 3: Regressed standard curve of Nateglinide in SIF at (pH 6.8)

Table 5: Standard curve of Nateglinide in PBS (pH 7.4) at 210 nm

S. No.	Concentration (µg/ml)	Absorbance	Statistical Analysis
1.	2	0.078	Correlation Coefficient R^2= 0.99367 Straight line equation y= 0.09969x + 0.02937
2.	4	0.246	
3.	6	0.343	
4.	8	0.448	
5.	10	0.542	
6.	12	0.660	
7.	14	0.689	
8.	16	0.821	
9.	18	0.945	
10.	20	1.009	

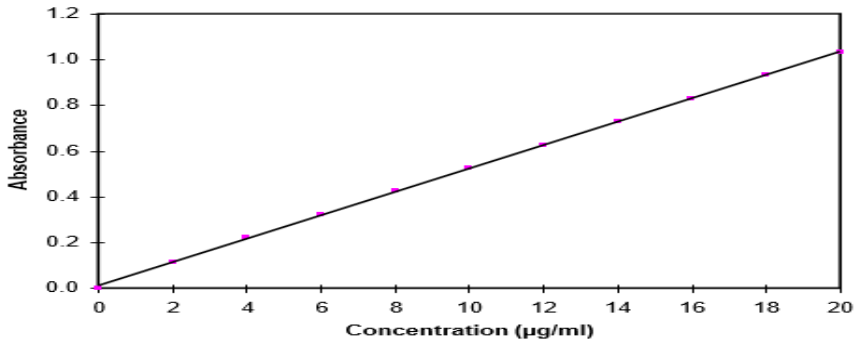


Figure 4: Regressed standard curve nateglinide in PBS (pH 7.4)

Table 6: Drug compatibilities studies with selected Polymers

S. No.	Composition	Maxima 210nm	Absorbance
1.	Drug	210	0.766
2.	Drug + PAA	210	0.713
3.	Drug + PVP	210	0.702

Table 7: Effect of PVP-PAA concentration on particle size and Shape of microspheres

Formulation code	Polymer (PVP-PAA) concentration (%W/V)	Particle size (µm)	Particle Shape
P1	0.1:1	98.2±2.6	Circular with rough surface
P2	0.2:1	109.4±2.5	Circular with smooth surface
P3	0.3:1	115.2±1.9	Nearly circular
P4	0.4:1	140.3±2.3	Deformed

Mean± SD (n =3)

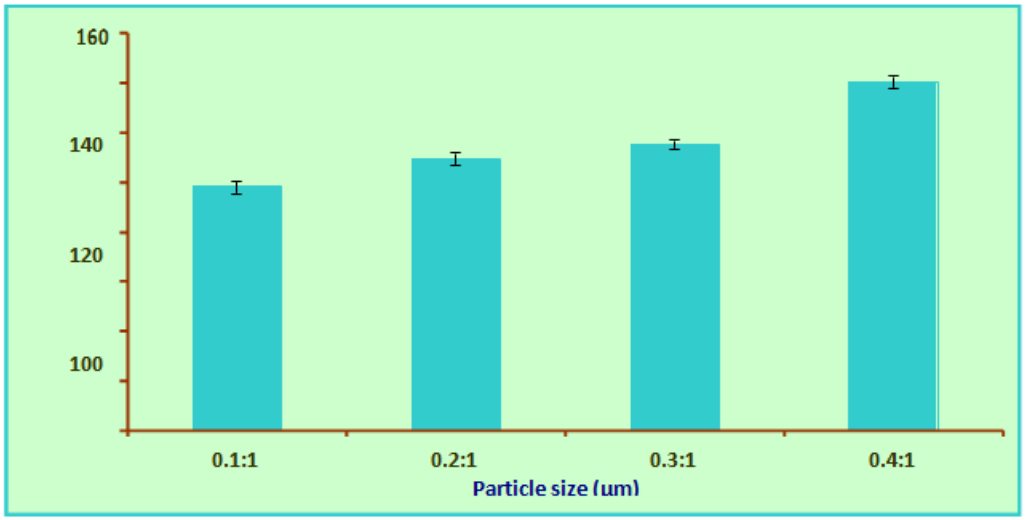


Figure 5: Effect of PVP-PAA concentration on particle size and drug loading of microspheres

Table 8: Effect of drug concentration on particle size and drug loading of microspheres

Formulation code	Drug concentration(% of polymer weight)	Particle size (µm)	% Drug loading
P2D1	20	105.4±1.8	79.8±1.5
P2D2	**40**	**113.2±2. 6**	**92.2±1.8**
P2D3	60	120.4±2.9	80.5±1.4
P2D4	80	123.5±3.1	72.2±2.2

Mean SD ± (n=3)

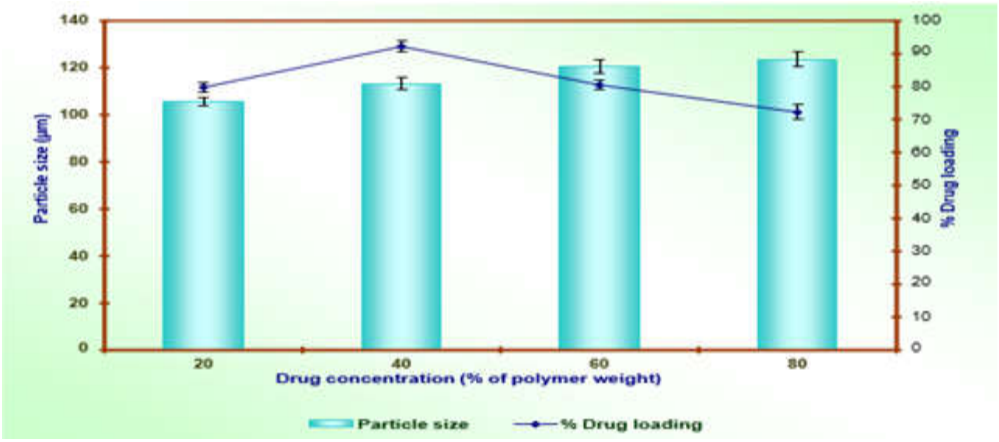


Figure 6: Effect of Nateglinide concentration (% of polymer weight) on particle size and drugloading of microspheres

Table 9: Effect of Phase ratio on particle size and drug loading

Formulation code	Phase ratio	Particle size (µm)	Percentage drug loading
P2D2I1	1:1	105.7±1.4	83.4±3.1%
P2D2I2	1:5	**109.2±2.5**	**93.3±2.8%**
P2D2I3	1:10	115.4±1.9	75.4±1.6%

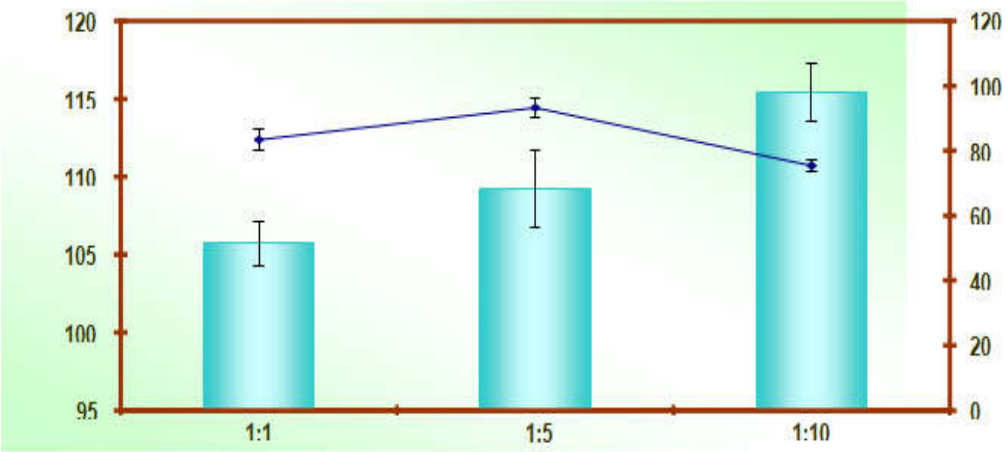


Figure 7: Effect of solvent ratio on particle size and drug loading

Table 10: Effect of surfactant concentration on particle size and drug loading

Formulation code	Surfactant conc. (% V/V)	Particle size (µm)	Percentage drug loading
P2D2I2E1	0.5	129.4±2.9	78.5±3.2%
P2D2I2E2	1.0	118.2±3.4	80.2±3.4%
P2D2I2E3	**1.5**	**113.6±2.4**	**92.8±1.6%**
P2D2I2E4	2.0	107.8±3.4	79.7±1.9%

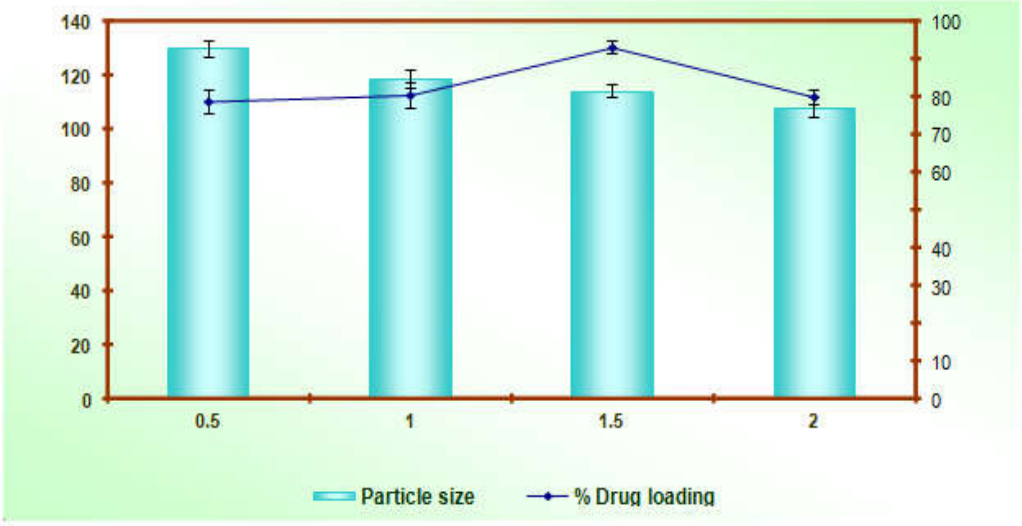


Figure 8: Effect of surfactant concentration on particle size and drug loading

Table 11: Effect of stirring speed on particle size and drug loading

Formulation code	Speed (rpm)	Particle size (µm)	Percentage drug loading
P2D2I2E3S1	300	137.4±5.2	75.8±.3.9%
P2D2I2E3S2	400	130.4±3.5	81.1±3.2%
P2D2I2E3S3	**500**	**111.2±3.7**	**91.3±2.5%**
P2D2I2E3S4	600	98.8±5.3	72.3±2.2%

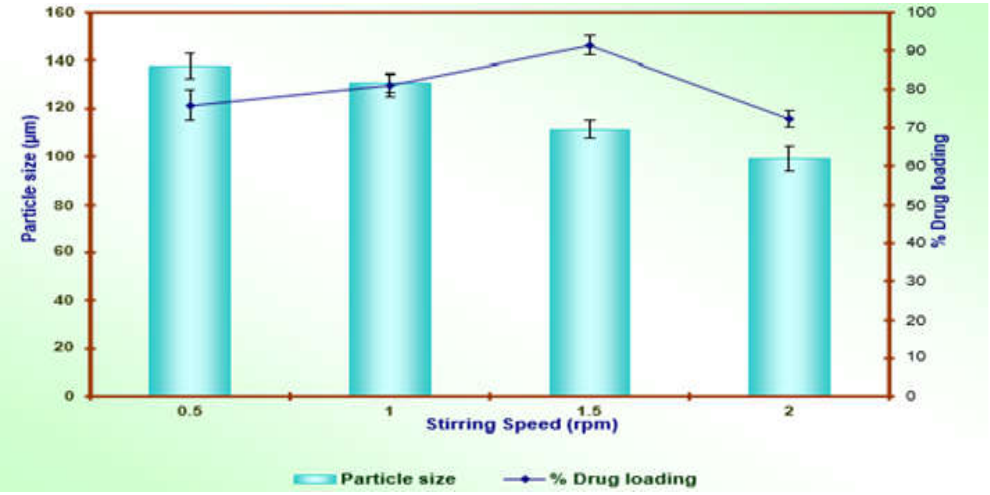
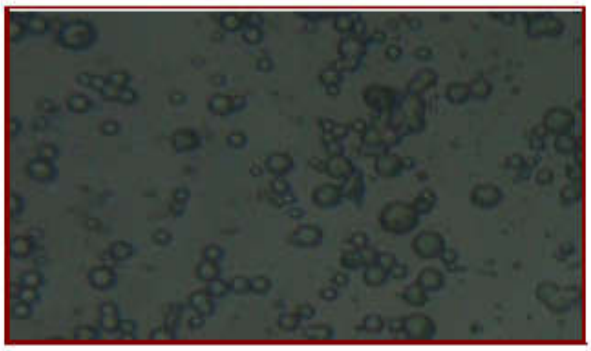


Figure 9: Effect of stirring speed on particle size and drug loading

Table 12: The optimized variables for the preparation of microspheres were selected as follows

S. No.	Variables	Optimized value	Final code foroptimized preparation
1.	Conc. Of PVP-PAA	0.2:1	P2D2I2E3S3T4
2.	Drug concentration	40 mg	
3.	Internal phase/external phase ratio	1:5	
4.	Surfactant concentration	1.5 (% v/v)	
5.	Stirring speed	500rpm	
6.	Stirring time	4hrs	



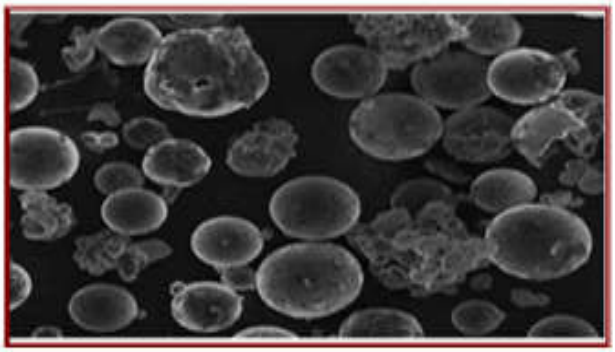


Figure 10: Photograph of PAA-PVP microspheres (100X) **Figure 11: SEM photomicrograph of PAA-PVP microspheres (650X)**

Table 13: Characteristic of optimized (P2D2I2E3S3T4) microspheres formulation

S. No.	Formulation	Particle size (µm)	Particle shape	Drug loading (%)
1.	P2D2I2E3S3T4	**109.32±2.3**	Circular shape	91. 3 ± 1.2%

Mean S.D. ± (n=3)

Table 14: Degree of swelling of PAA-PVP microspheres

S. No.	Microspheres	Formulation Code	Degree of Swelling(after 8hrs)
1.	PAA-PVP microspheres	**P2D2I2E3S3T4**	2.84

Table 15: *In vitro* Wash-off Test of PAA-PVP microspheres

S. No.	*In vitro* wash of time(in hrs)	% Mucoadhesion
1	1	78
2	5	72
3	10	62

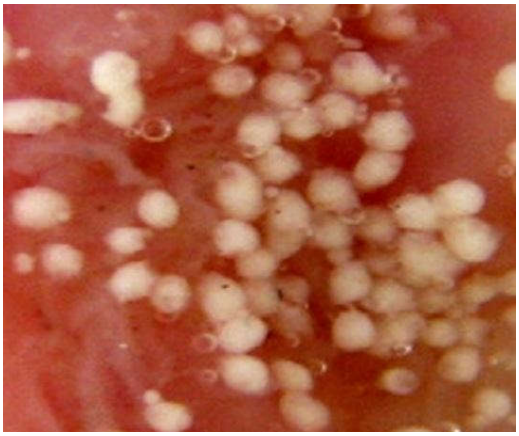


Figure 12: *In vitro* wash-off test of Nateglinide loaded mucoadhesive microspheres after 10hr

Table 16: % cumulative Nateglinide release from PAA-PVP microspheres in different pH ofbuffer medium

S No.	Time interval (hrs)	SGF (pH 1.2)	SIF (pH 6.8)	PBS (pH 7.4)
1	0.5	8.5±0.9	9.1±2.2	10.2±1.2
2	1	13.6±1.4	14.3±1.3	16.3±2.3
3	2	23.3±2.3	20.3±1.7	22.3±2.9
4	3	33.6±3.1	31.4±2.1	33.4±2.5
5	4	42.2±3.4	39.5±1.2	45.5±3.1
6	5	52.6±3.2	57.5±2.1	63.5±2.7
7	6	63.7±3.1	68.6±2.5	72.6±3.7
8	7	70.2±3.5	75.1±1.8	79.7±3.8
9	8	78.3±3.2	80.4±2.6	83.8±3.4
10	24	87.4±3.8	89.3±1.4	93.6±3.2

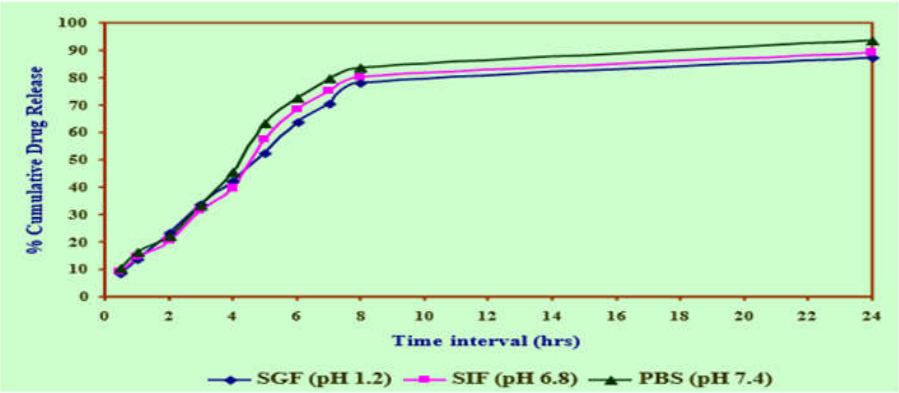


Figure 13: % cumulative nateglinide release from PAA-PVP microspheres in different pH of buffer medium

CONCLUSION

The result obtained from all the experiments perform as a part of project work suggested that it is possible to prepare an gastroretentive and sustained release mucoadhesive microspheres preparation using combination of PAA-PVP polymers by interpolymer complexation and solvent diffusion method. Mucoadhesive microspheres drug delivery system provides the possibility of enhancing the bioavailability and control the release of Nateglinide exhibiting absorption window by prolonging the gastric emptying time of the dosage form ensuring availability of drug at the absorption site for the desired period of time. As the Mucoadhesive microspheres showed a good mucoadhesion and drug release properties sothat it has a great potential for its use both in powder form for drysuspension and granular form for tableting.

DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

REFERENCES

- Behera, B.C., Sahoo, S.K., Dhal, S., Barik, B.B. & Gupta, B.K. (2008) Characterization of glipizide-loaded polymethacrylate microspheres prepared by an emulsion solvent evaporation method. *Tropical Journal of Pharmaceutical Research*, 7, 879–885.
- Belgamwar, V., Shah, V. & Surana, S.J. (2009) Formulation and evaluation of oral mucoadhesive multiparticulate system containing metoprolol tartarate: An *in vitro-ex vivo* characterization. *Current Drug Delivery*, 6, 113–121.
- Bera, K., Khanam, J., Mohanraj, K.P. & Mazumder, B. (2014) Design and evaluation of mucoadhesive beads of glipizide as a controlled release drug delivery system. *Journal of Microencapsulation*, 31, 220–229.
- Chun, M.K., Cho, C.S. & Choi, H.K. (2005) Mucoadhesive microspheres prepared by interpolymer complexation and solvent diffusion method. *International Journal of Pharmacy*, 20, 288–295.
- Deshpande, A.A., Shah, N.H., Rhodes, C.T. & Malick, W. (1997) Development of novel controlled release system for gastro retention. *Pharmaceutical Research*, 14, 815–819.
- Hanefeld, M., Bouter, K.P., Dickinson, S. & Guitard, C. (2000) Rapid and short-acting mealtime insulin secretion with nateglinide controls both prandial and mean glycemia. *Diabetes Care*, 23, 202–207.
- Iannuccelli, V., Coppi, G., Bernabei, M.T. & Cameroni, R. (1998) Air compartment multiple-unit system for prolonged gastric residence. Part I. Formulation study. *International Journal of Pharmaceutics*, 174, 47–54.
- Jaimini, M., Rana, A.C. & Tanwar, Y.S. (2007) Formulation and evaluation of famotidine floating tablets. *Current Drug Delivery*, 4, 51–55.
- Jain, S., Bhandari, A. & Purohit, S. (2009) Spectrophotometric

determination of nateglinide in bulk and tablet dosage forms. *Asian Journal of Pharmaceutics*, 3, 218–221.

- Klausner, E.A., Lavy, E., Friedman, M. & Hoffman, A. (2003) Expandable gastroretentive dosage forms. *Journal of Controlled Release*, 90, 143–162.
- Patel, J.K., Patel, R.P., Amin, A.F. & Patel, M.M. (2005) Formulation and evaluation of mucoadhesive glipizide microspheres. *AAPS PharmSciTech*, 6, E49–E55.
- Streubel, A., Siepmann, J. & Bodmeier, R. (2003) Multiple unit Gastroretentive drug delivery: A new preparation method for low density microparticles. *Journal of Microencapsulation*, 20, 329–347.
- Vyas, S.P. & Khar, R. (2006) Ks. gastroretentive systems. In: *Controlled Drug Delivery*. Vallabh Prakashan. Delhi, India, pp. 197–217.