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Research Article

Development And Characterization Of Liposphere Of Antidiabetic Drug Nateglinide For Enhance Bioavailability

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ABSTRACT

The aim of this study was to develop and characterize lipospheres of the antidiabetic drug. Nateglinide to enhance its bioavailability. Nateglinide, a poorly water-soluble drug, poses challenges in achieving optimal therapeutic effects due to its limited solubility and bioavailability. Lipospheres, lipid-based drug delivery systems, offer a promising approach to overcome these challenges by enhancing drug solubility and bioavailability. In this research, lipospheres of Nateglinide were prepared using a solvent evaporation method with various lipids and surfactants. The formulated lipospheres were characterized for their physicochemical properties, including particle size, morphology, encapsulation efficiency, and drug release profile. Additionally, the in vitro dissolution studies and pharmacokinetic parameters of the optimized liposphere formulation were evaluated. The results demonstrated successful formulation of Nateglinide-loaded lipospheres with uniform particle size distribution and high encapsulation efficiency. Scanning electron microscopy revealed spherical morphology with smooth surfaces. In vitro dissolution studies showed enhanced dissolution rates compared to the pure drug, indicating improved solubility and release characteristics. The developed lipospheres of Nateglinide offer a promising strategy for enhancing the bioavailability and therapeutic effectiveness of this antidiabetic drug. The lipid-based formulation provides enhanced solubility, controlled release, and improved pharmacokinetic profile, thereby potentially improving patient compliance and treatment outcomes in the management of diabetes mellitus.

INTRODUCTION

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.1 Nateglinide interacts with the ATPsensitive potassium (K+ATP) channel on pancreatic beta-cells. The subsequent depolarization of the beta cell opens the calcium channel, producing calcium influx and insulin

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secretion.2 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.3 The drug is widely used for the management of type-2 diabetes. It has short biological half life (1.5 ± 0.7 h) and bioavailability is 73%. The conventional therapies to treat existent diabetes consist of complex drug regimen that leads to increased pill burden, frequent and high daily dosing, and dose-associated side effects and ultimately results in poor patients' compliance with worsening of such patients' condition. 4,5 Lipospheres can enhance patient's compliance by reducing drug dosing frequency, lowering adverse effects, and limiting fluctuation in plasma drug levels.6 Size of lipospheres varies from 1 to 1000 µm, and various methods like solvent evaporation, spray drying, ionotropic gelation, coacervation, and melt emulsification congealing method have been employed for lipospheres preparation.7 Lipids have exhibited efficient biodegradability, biocompatibility, and ease of utilization in production process due to their lower melting points. 8,9 So, the idea of sustained delivery of an antidiabetic agent was generated because the mode of drug administration has been contributing a lot in improving therapeutic efficacy and decreasing adverse effects of a drug. So, to overcome noncompliance, discovery of novel controlled release methods of drug delivery like lipospheres for delivery of drug has been proven to be more beneficial. So aim of present work to formulate and evaluates Nateglinide loaded lipospheres for effective absorption and increase bioavailability.

MATERIAL AND METHODS

Preformulation Studies

Characterization of Nateglinide

Physical evaluation: It refers to the evaluation by sensory characters-taste, appearance, odor, feel of the drug, etc.

Table 01: List of Sensory characters

Sr. No.	Sensory characters	Result
1.	Color	White to off-white powder
2.	Odor	Mild
3.	Appearance	Solid fine powder

Solubility:

Solubility of the drug was determined by taking some quantity of drug (about 1-2 mg) in the test tube separately and added the 5 ml of the solvent (Water, ethanol, methanol, 0.1 N HCl, 0.1 N NaOH, chloroform and phosphate buffer pH 6.8) Shake vigorously and kept for some time. Note the solubility of the drug in various solvents (at room temperature). 10

Table 02: Solubility of Nateglinide

Solvent used	Solubility of Nateglinide
Distilled water	+
0.1 N Hydrochloric acid	+++
Ethanol	++++
Methanol	++++
Chloroform	+++
0.1 N NaOH	+

Melting point:

It is one of the parameters to judge the purity of drugs. In case of pure chemicals, melting points

are very sharp and constant. Since the drugs contain the mixed chemicals, they are described with certain range of melting point.

Identification test using FT-IR Spectroscopy: Infra- red spectrum is an important record which gives sufficient information about the structure of a compound. This technique provides a spectrum containing a large number of absorption band from which a wealth of information can be derived about the structure of an organic compound. The region from 0.8 µ to 2.5 µ is called Near Infra-red and that from 15 µ to 200 µ is called Far infra-red region. Identification of Nateglinide was done by FTIR Spectroscopy with respect to marker compound. Nateglinide was obtained as white powder.

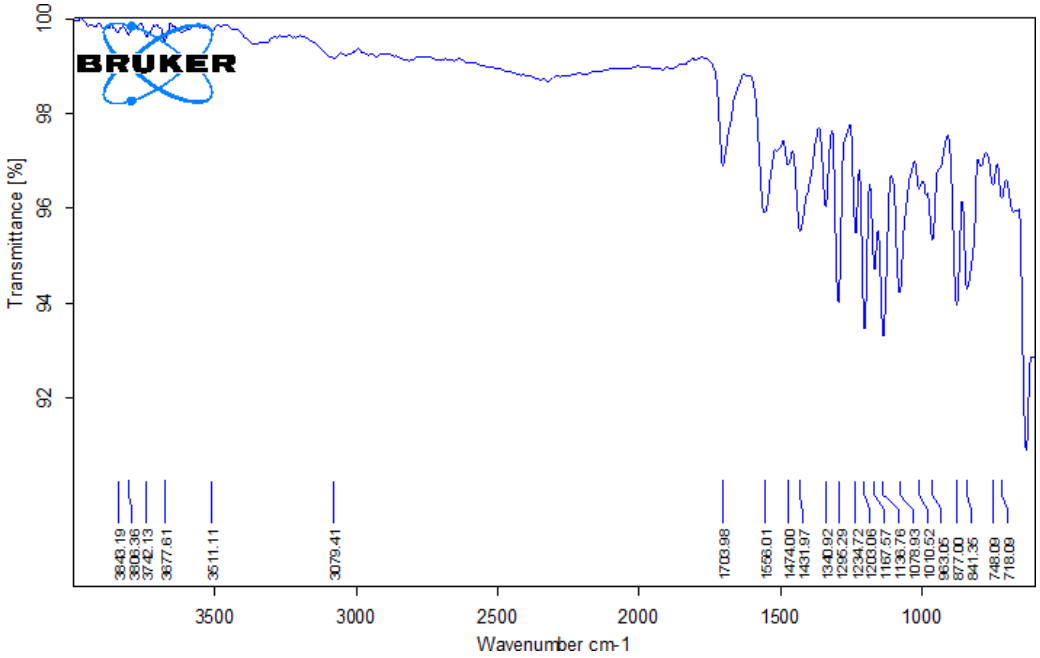

Figure 01: FT-IR spectrum of Nateglinide

Loss on drying:

The moisture in a solid can be expressed on a wet weight or dry wet basis. On a wet weight basis, the water content of a material is calculated as a percentage of the weight of the weight solid. The term loss on drying is an expression of moisture content on a wet weight basis.

Moisture content determination:

The titrimetric determination of water is based upon the quantitative reaction of water with an anhydrous solution of sulphur dioxide and iodine in the presence of a buffer that reacts with hydrogen ions.

Determination of λ max of Nateglinide

The λmax of Nateglinide was determined by running the spectrum of drug solution in double beam ultraviolet spectrophotometer.

Table 03: Calibration curve of Nateglinide in phosphate buffer 0.1 N HCl

Sr. No.	Concentration (µg/ml)	Absorbance
1	2	0.145
2	4	0.295
3	6	0.466
4	8	0.638
5	10	0.832

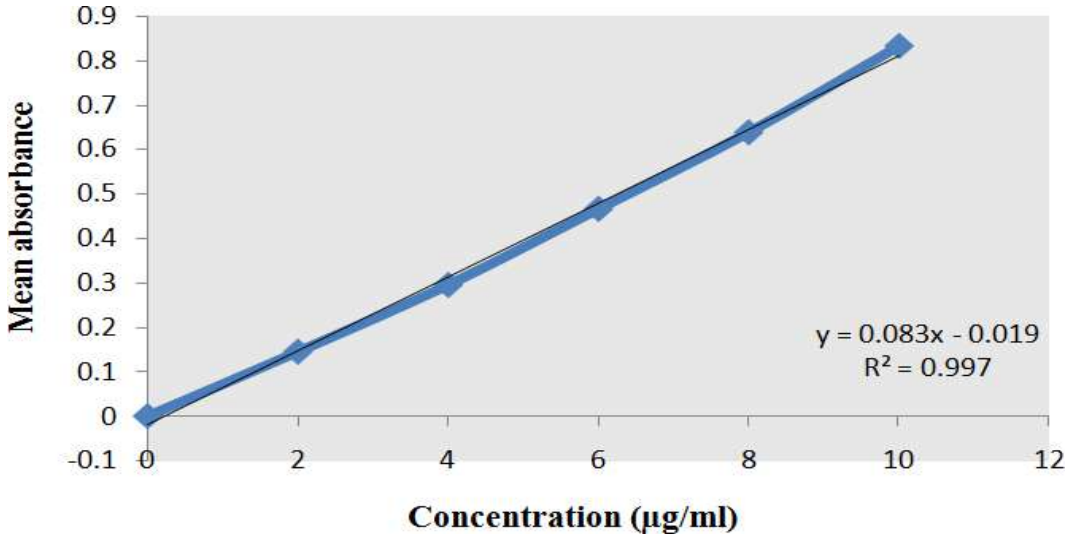

Figure 02: Calibration curve of Nateglinide

Formulation development of Lipospheres:

Drug encapsulated Lipospheres were developed by melt dispersion technique. 11 The formulation of different batches is depicted in Table 04. Briefly, the lipid core was melted on a water bath maintained at 70-72°C. Finely powdered drug was dispersed into the molten lipidic phase. The aqueous phase was prepared by heating a blend of water and surfactant to 70-72°C with a stabilizer. The molten lipidic phase was slowly transferred to the hot aqueous phase (o/w emulsion) and the emulsification was assisted by stirring the content on a sonicator continuously. The milky dispersion was then rapidly cooled to 20°C by immersing the formulation in an ice bath without stopping the agitation to yield a uniform dispersion of lipospheres. The obtained lipospheres were then washed with water and isolated by filtration.

Table 04: Preparation of Liposphere of Nateglinide

Formulation Code	Nateglinide (mg)	Lipid core (mg)		Tween 80 (ml)	Gelatin (mg)	Water (ml)
		Stearic acid (mg)	Cetyl alcohol (mg)			
F1	60	100	400	1.5ml	2	100
F2	60	150	350	1.5ml	2	100
F3	60	200	300	1.5ml	2	100
F4	60	250	250	1.5ml	2	100
F5	60	300	200	1.5ml	2	100
F6	60	350	150	1.5ml	2	100

Characterization of Nateglinide encapsulated lipospheres

Percentage Yield of Lipospheres:

Yield of Lipospheres percent w/w is calculated according to the following formula:

% Yield = Weight of lipospheres /Wt. of Drug + Wt. of Excipients

Drug loading and Entrapment efficiency 12

The amount of Nateglinide present in lipospheres is determined by taking the known amount of lipospheres in which 10mg of drug should be present theoretically. Then the lipospheres crush and the powdered microspheres are taken and dissolve in 10 ml of methanol and stirred for 15 minutes with an interval of 5 minutes and allow keeping for 24 hours. Then the solution was filtered through whatmann filter paper. Then the

absorbance after appropriate dilution was measured spectrophotometrically at 244nm by UV-Visible spectrophotometer.

Drug entrapment efficiency (%) = (Experimental drug content/Initial drug content in the formulation) × 100

Measurement of mean particle size

The mean size of the lipospheres was determined by Photo Correlation Spectroscopy (PCS) on a submicron particle size analyzer (Malvern Instruments) at a scattering angle of 90°. A sample (0.5mg) of the lipospheres suspended in 5 ml of distilled water was used for the measurement. 13

Determination of zeta potential:

The zeta potential of the drug-loaded lipospheres was measured on a zeta sizer (Malvern zetasizer instruments) by determining the electrophoretic mobility in a micro electrophoresis flow cell. All the samples were measured in water.

Surface morphology (Scanning electron microscopy):

Morphology and surface topography of the lipospheres were examined by scanning electron microscopy. The lipospheres from the optimized batch were mounted on the SEM sample stab using a double-sided sticking tape and coated with gold (~200 nm) under reduced pressure (0.133 Pa) for 5 min using an Ion sputtering device. The gold coated lipospheres were observed under the scanning electron microscope and photomicrographs of suitable magnifications were obtained.

Flow property determination of the Lipospheres: Bulk density:

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. Accurately weighed amount of granules taken in a 50 ml capacity measuring cylinder was tapped for 100 times on a plane hard wooden surface and estimated the LBD and TBD, calculated by using following formulas. 14

$$\text{LBD (Loose Bulk Density)} = \frac{\text{Mass of Powder}}{\text{Volume of Packing}}$$

$$\text{TBD (Tapped Bulk Density)} = \frac{\text{Mass of Powder}}{\text{Tapped Volume of Packing}}$$

Table 05: Grading of flow properties according to Carr's Index

Sr. No.	Carr's Compressibility index	Flow
1.	5 – 15	Excellent
2.	12 – 16	Good
3.	*18 – 21	Fair to passable
4.	*23 – 35	Poor
5.	33 – 38	Very poor
6.	>40	Very very poor

Adding glidant e.g. Talc should improve the flow properties

In-vitro drug release studies: The dissolution of Nateglinide from the prepared lipospheres was monitored using USP XXV paddle II apparatus. The Amount of the lipospheres equivalent to 10 mg of Nateglinide was dispersed into the dissolution medium. The dissolution media was 900 ml of pH 1.2 buffer maintained at 37±0.5ºC and rotating at 50±1 rpm. The 5ml aliquots were withdrawn at pre-determined time intervals and the withdrawn samples were replaced with fresh dissolution medium. The samples were then analyzed spectrophotometrically at 244.0 nm for Nateglinide. 14

RESULTS AND DISCUSSION

Characterization of Nateglinide encapsulated lipospheres

Percentage Yield of lipospheres: Yield of lipospheres percent w/w was calculated according to the following formula:

% Yield = Weight of lipospheres /Wt. of Drug + Wt. of Excipients× 100

Table 06: Percentage yields of lipospheres

Formulation Code	% Yield
F1	68.85±0.32
F2	65.95±0.41
F3	70.23±0.15
F4	75.65±0.23
F5	63.32±0.26
F6	65.85±0.17

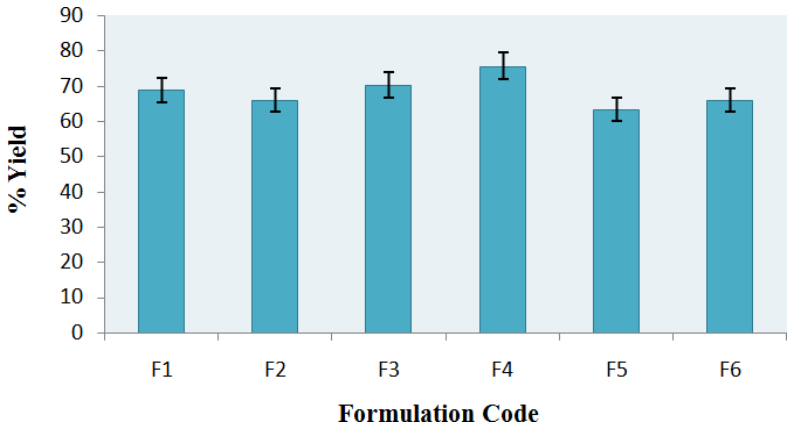

Figure 03: Percentage yields of lipospheres

Drug loading and Entrapment efficiency:

Table 07: % Drug entrapment efficiency

Formulation Code	% Drug entrapment efficiency
F1	65.58±0.32
F2	63.32±0.25
F3	69.85±0.15
F4	73.32±0.41
F5	64.41±0.36
F6	65.85±0.22

Microscopic Evaluation:

An optical microscope (MSW) with a camera attachment (Olympus) was used to observe the shape of the prepared liposphere formulation F4.

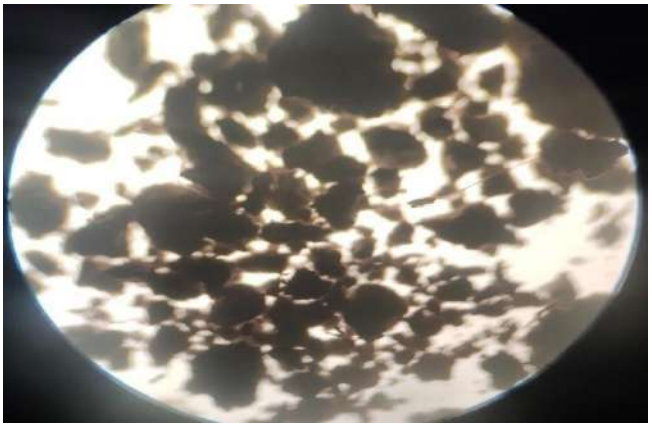

Figure 04: Microscopic observation of prepared optimized liposphere formulation F4

Particle size:

The mean size of the lipospheres was determined by photo correlation spectroscopy (PCS) on a submicron particle size analyzer (Horiba Instruments) at a scattering angle of 90°. A sample (0.5mg) of the lipospheres suspended in 5 ml of distilled water was used for the measurement. The results of measurement of mean particle size of optimized formulation F4 lipospheres were found 196.65 nm.

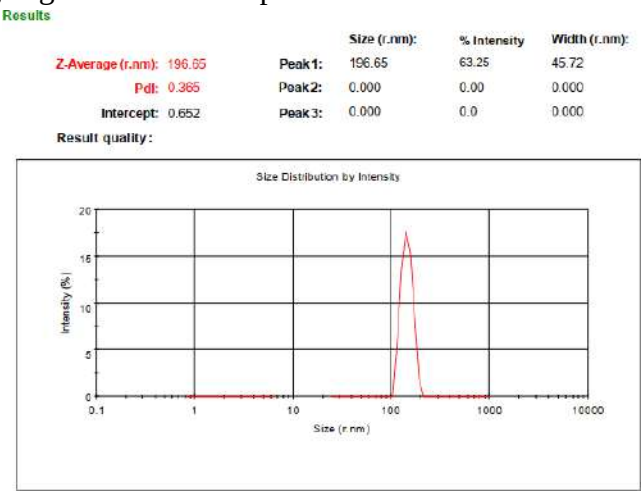

Figure 05: Particle size data of lipospheres

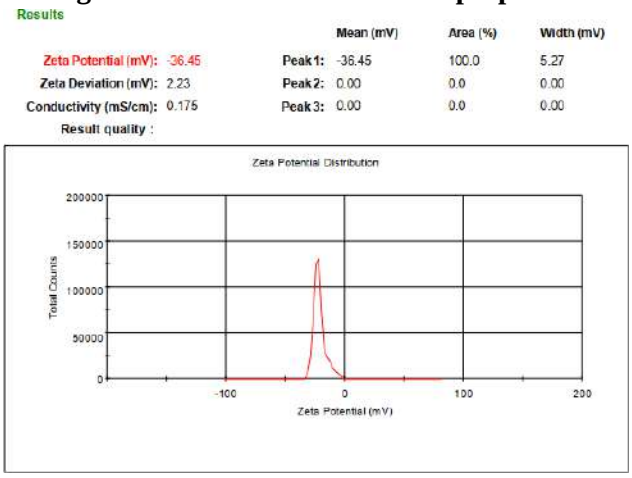

Figure 06: Zeta potential data of lipospheres

Zeta Potential:

The zeta potential of the drug-loaded lipospheres was measured on a zeta sizer (Malvern Instruments) by determining the electrophoretic mobility in a micro electrophoresis flow cell. All the samples were measured in water Results of zeta potential of optimized formulation F4 lipospheres was found -36.45 mV respectively.

Scanning electron microscopy: Morphology and surface topography of the lipospheres were examined by scanning electron microscopy. The lipospheres from the optimized batch were mounted on the SEM sample stab using a double-sided sticking tape and coated with gold (~200 nm) under reduced pressure (0.133 Pa) for 5 min using an Ion sputtering device. The gold coated lipospheres were observed under the scanning electron microscope and photomicrographs of suitable magnifications were obtained.

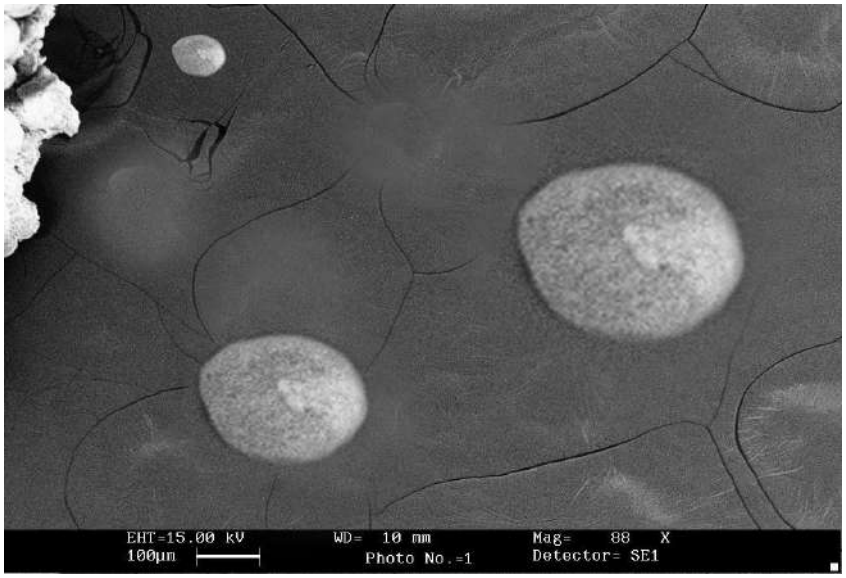

Figure 07: SEM Image of Optimized Formulation F4

Table 08: Result of Flow Properties of prepared Formulations

Formulation code	Parameters			
	Loose Bulk density(gm/ml)	Tapped bulk density(gm/ml)	Carr's Index (%)	Hausner's Ratio
F1	0.385	0.495	22.22	1.286
F2	0.365	0.473	22.83	1.296
F3	0.374	0.485	22.89	1.297
F4	0.352	0.462	23.81	1.313
F5	0.374	0.482	22.41	1.289
F6	0.368	0.469	21.54	1.274

The loose bulk density (LBD) and Tapped bulk density (TBD) of the powders of different formulations were evaluated before the compression of powders in to tablets. The bulk density and the tapped density for all the formulations varied from 0.352 to 0.374gm/cm3 and 0.462 to 0.495gm/cm3 respectively. The values obtained lies within the acceptable range. The difference exists between the bulk density and tapped density found to be very few. This result helps in calculating the % compressibility of the powder. The result of Hausner's ratio of all formulations ranges from 1.274 to 1.313. Results of Hausner's ratio of all formulations were shown in Table no 8.4 which indicates that the flow ability of all the formulation. The results of the Compressibility index of all the formulations ranges from 22.22% to 23.81%. Results clearly showed that the flow ability of all the formulations was good and also the powder had good compressibility

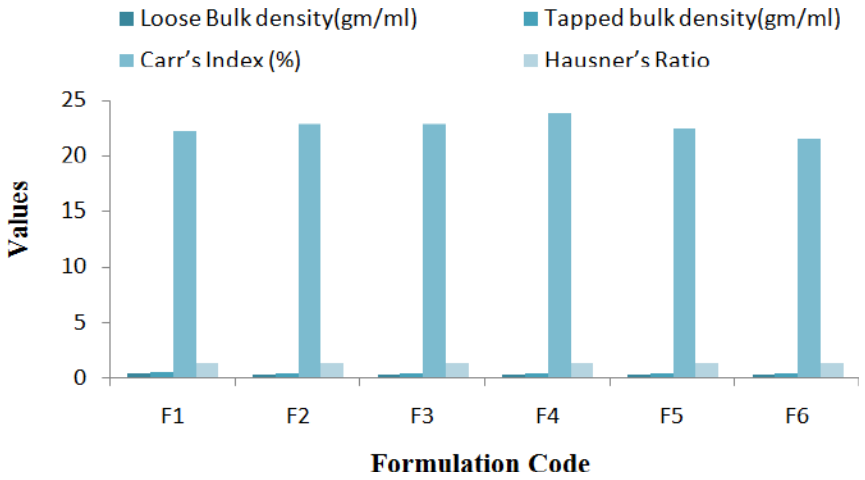

Figure 08: Graph of Flow Properties of prepared Formulations

In vitro drug release study of Nateglinide loaded optimized formulation F4 :

Table 09: Release study of Formulation F4

Time (h)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative*% Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
0.5	0.707	-0.301	22.15	1.345	77.85	1.891
1	1	0	36.65	1.564	63.35	1.802
1.5	1.414	0.301	45.52	1.658	54.48	1.736
2	1.732	0.477	52.23	1.718	47.77	1.679
3	2	0.602	65.52	1.816	34.48	1.538
4	2.449	0.778	73.32	1.865	26.68	1.426
6	2.828	0.903	79.98	1.903	20.02	1.301
8	3.162	1	86.65	1.938	13.35	1.125
10	3.464	1.079	95.65	1.981	4.35	0.638
12	4.899	1.38	99.12	1.996	0.88	-0.056

Release Kinetics of Nateglinide loaded optimized formulation F4 Zero order release kinetics of optimized formulation:

Table 10: Zero order release kinetics of optimized formulation

Sr. No.	Time (Hrs.)	Cumulative*% Drug Release
1	0.5	22.15
2	1	36.65
3	1.5	45.52
4	2	52.23
5	3	65.52
6	4	73.32
7	6	79.98
8	8	86.65
9	10	95.65
10	12	99.12

The In vitro drug release data of the optimized formulation was subjected to goodness of fit test by linear regression analysis according to zero order and first order kinetic equation, Higuchi's

and Korsmeyer's models in order to determine the mechanism of drug release. When the regression coefficient values of were compared, it was observed that 'r' values of Korsmeyer peppas was maximum i.e 0.959, Hence, indicating drug release from formulations was found to follow Korsmeyer peppas r release kinetics.

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