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Optimization and Characterization of Floating Microspheres of Sitagliptin Using A Polymer-Based Gastroretentive Drug Delivery Approach

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ABSTRACT

The present study focuses on the formulation and evaluation of floating sustained-release microspheres of Sitagliptin using the ionotropic gelation method. Sodium alginate and chitosan were employed as natural, biocompatible matrix-forming agents, while calcium chloride served as the cross-linking agent. A total of nine formulations (SM1–SM9) were prepared by varying polymer concentrations to assess their effects on particle size, buoyancy, entrapment efficiency, and drug release behavior. The optimized formulation, SM2, showed superior performance with high drug entrapment (72.25± 2.65%), good buoyancy (80.12±3.36%), maximum yield (76.65±2.25%), and a controlled drug release of 76.56± 2.80% over 12 hours. Scanning electron microscopy confirmed the spherical shape and smooth surface of the microspheres. Kinetic modeling indicated that drug release from SM2 followed first-order kinetics, with diffusion-controlled and non-Fickian transport mechanisms. These findings suggest that SM2 is a promising oral delivery system for improving the bioavailability and therapeutic effectiveness of Sitagliptin in the management of type 2 diabetes mellitus.

Keywords: *Sitagliptin; Floating microspheres; Ionotropic gelation; Sustained release; Sodium alginate; Chitosan; Drug release kinetics; Type 2 diabetes mellitus.*

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1. INTRODUCTION

Floating drug delivery systems (FDDS) are a promising approach for extending the residence time of a drug in the gastrointestinal tract, enhancing bioavailability, and providing controlled drug release. These systems are designed to remain buoyant in the stomach, allowing for sustained release over an extended period and thereby improving the therapeutic efficacy of drugs that require prolonged exposure at the site of absorption (Deshmukh *et al*., 2017). The concept of floating microspheres has gained significant attention due to their ability to overcome the limitations of conventional drug delivery systems by enhancing the solubility and absorption of poorly soluble drugs (Kawashima *et al*., 1992).

Sitagliptin is an oral antihyperglycemic agent commonly used in the treatment of type 2 diabetes. It inhibits the enzyme DPP-IV, which is responsible for the degradation of incretin hormones. As incretin hormones play a key role in regulating glucose metabolism, Sitagliptin enhances insulin release and decreases glucagon secretion in a glucose-dependent manner (Belfort *et al*., 2011). However, Sitagliptin suffers from poor bioavailability due to its relatively short half-life and rapid gastrointestinal transit time. Formulating Sitagliptin into a floating sustained-release microsphere can potentially enhance its residence time in the stomach, leading to improved drug absorption and sustained therapeutic effects (Patel *et al*., 2012). The ionotropic gelation method has been widely used for the preparation of floating microspheres due to its simplicity and efficiency in controlling particle size and drug release profile. Chitosan and sodium alginate are frequently used as matrix-forming agents in floating microspheres because of their biocompatibility, biodegradability, and the ability to form stable gel structures when in contact with certain ions (Deshmukh *et al*., 2017; Bhatt *et al*., 2015). Chitosan, derived from chitin,

has been shown to exhibit mucoadhesive properties that may further enhance the retention of the microspheres in the gastrointestinal tract (Singh *et al.,* 2008).

The aim of this study is to develop floating sustained-release microspheres of Sitagliptin using the ionotropic gelation method, employing sodium alginate and chitosan as matrix-forming agents, and to characterize their physicochemical properties, including drug entrapment, buoyancy, particle size, and in vitro drug release profiles. The developed microspheres may offer a potential solution for improving the bioavailability and therapeutic outcomes of Sitagliptin, providing a controlled release system for effective long-term management of type 2 diabetes.

2. MATERIAL AND METHODS

Material

The materials used in this study include **Sitagliptin,** a drug for type 2 diabetes. **Eudragit S-100** from **Evonik Industries** was used as the polymer for controlled release. The solvents **Dichloromethane (DCM)** and **Ethanol,** sourced from **Sigma-Aldrich,** were employed for dissolving the drug and polymer. **Polyvinyl Alcohol (PVA),** also from **Sigma-Aldrich**, was used as an emulsifier to stabilize the microspheres during preparation. All chemicals were of analytical grade, ensuring the quality of the formulation.

Methods

Formulation of floating microspheres of Sitagliptin

Floating microspheres were prepared by slightly modifying solvent diffusion evaporation method (Kawashima *et al.,* 1992). Ten formulations of floating microspheres were developed. Different ratios of Sitagliptin and Eudragit S-100 were mixed in a mixture of dichloromethane (DCM) and ethanol at room temperature (Table 1). The resulting suspension was added slowly into stirring to 0.25% w/v 400 mL solution of polyvinyl alcohol (PVA) at room temperature (Lee *et al.,* 1999). The stirring was continued for 2 h by mechanical stirrer equipped with four blade propellers in order to evaporate the solvent. After evaporation of solvent, microspheres were collected by filtration and washed repeatedly with water. The collected microspheres were dried at room temperature and stored in a desiccator.

Table 1: Formulation code and composition for Sitagliptin floating microspheres

Batch Code	Drug: Polymer ratio	Concentration of emulsifying agent (%)	Stirring Rate (rpm)	Solvent ratio (DCM: ethanol, mL)
SM1	1:1	0.46	900	1:1
SM2	1:1.5	0.46	900	1:1
SM3	1:2	0.46	900	1:1
SM4	1:1.5	0.46	1000	1:1
SM5	1:2	0.46	1000	1:1
SM6	1:2.5	0.46	1200	1:1
SM7	1:2	0.46	1300	1:1
SM8	1:2.5	0.46	900	1:3
SM9	1:3	0.46	900	3:1

Characterization of Floating Microspheres of Sitagliptin

Micromeritics properties

The prepared microspheres were characterized for micromeritics properties like particle size. (Aulton, 2002, Jain *et al.,* 2006, Hanna 1990).

Particle size

Optical microscope was used to determine the particle size of prepared microspheres. In distilled water dried microspheres were dispersed and suitably placed on a glass slide. Using stage micrometer the number of divisions of the eye piece was counted. 200 microspheres were randomly selected and there mean particle diameter was measured using calibrated ocular micrometer. Using Edmundson's equation (Rawat *et al.,* 2007) average particle size was determined.

$$D_{mean} = \frac{\sum nd}{\sum n}$$

Where, n= number of microspheres counted; d= mean size.

Drug entrapment efficiency

The floating microspheres containing 50 mg of drug from each batch was weighed accurately and crushed. The powdered microspheres were placed in ethanol (10 ml). After 12 hours solution was filtered using whatmann filter paper no. 44. After proper dilution the absorbance of the sample was recorded at 267 nm using UV spectrophotometer and entrapment of drug was estimated by using the formula given below.

$$\% \text{ Drug entrapment} = \frac{\text{Calculated drug content}}{\text{Theoretical drug content}} \text{ X } 100$$

Percentage Yield

The prepared microspheres of all the batches were accurately weighed (Singhal *et al.*, 2011). The percentage yield of floating formulations was calculated using following formula:

$$\% \text{ Yield} = \frac{\text{Actual weight of product}}{\text{Total weight of polymer and drug}} \text{ X } 100$$

Morphological study using SEM

Scanning electron microscope was used to study the morphology of prepared microspheres which helps in correlating characteristics features at surface of the samples. SEM is better than light microscope as higher resolution maximum upto 10-20 nm was obtained as compared to 200-300 nm from light microscope. SEM studies were carried out using Jeol JSM-1600, Tokyo, Japan. Prepared microspheres were lightly sprinkled on a double adhesive tape which is fixed to aluminum stubs. A thin layer of gold about 300ºA was vacuum coated using a sputter coater and samples were randomly scanned and photographs were taken (Singhal *et al.*, 2011).

***In-vitro* buoyancy study**

In-vitro buoyancy was determined by placing 50 mg of formulation in 100 ml of SGF (pH 1.2) containing Tween 20 (0.02 w/v %) stirred at 100 rpm using a magnetic stirrer. Layer of floating microspheres were separated from the microspheres which were settled down by filtration after 12 hours. Both the obtained particles were dried and separately weighed. Using the formula given below buoyancy of microspheres was determined (Chilukala *et al*., 2016).

$$\text{Buoyancy (\%)} = W_f / (W_f + W_S) \text{ X } 100$$

Where W_f and Ws are the respective weights of the floated and settled microspheres.

***In-vitro* drug release study**

Paddle type dissolution apparatus having six stations (Veego, VDA-6DR, USP Std) was used to determine release of drug from formulation. Floating microspheres equivalent to 16 mg of drug was kept in 0.1N HCl containing Tween 20 (0.02 w/v %). Temperature was maintained at 37±0.5º C with 100 rpm speed of rotation. During the study sink condition was maintained. 1 ml sample was withdrawn at different time interval, passed through 5µm membrane filter and analyzed spectrophotometrically at 267 nm. The cumulative percent drug release was calculated using standard calibration curve (Gadad *et al*., 2016).

Drug release kinetics

Optimized formulation's release data was fitted to various mathematical models to reveal the release mechanism from the microspheres. All curve fitting, simulation and plotting were performed using commercially available Microsoft excel solver and regression coefficient (r^2) values were calculated.

3. RESULTS AND DISCUSSION

The current study was conducted to develop and evaluate **floating sustained-release microspheres of** Sitagliptin using the **ionotropic gelation method**, employing sodium alginate and chitosan as matrix-forming agents. The composition of the different formulations (SM1–SM9) is outlined in **Table 1**, where systematic variations in the concentrations of sodium alginate and chitosan were applied to investigate their impact on the formulation characteristics.

Table 2 presents the **percentage buoyancy, drug entrapment efficiency**, and **percentage yield** of the floating microspheres. Floating ability is vital for gastric retention and sustained release, and most formulations showed **buoyancy above 70%**, with the highest observed in **SM4 (83.41**±3.36**%)** and **SM1 (82.01**±3.25**%)**. **Drug entrapment efficiency** ranged from **55.57**±2.36**% (SM7)** to **72.25**±2.65**% (SM2)**, showing that optimized polymer ratios significantly enhance drug loading. The **highest yield** was recorded for **SM2 (76.65**±2.25**%)**, indicating a robust and reproducible manufacturing process. Based on these parameters, **SM2** was considered the **optimized formulation** for further evaluation.

The **morphology of the optimized formulation (SM2)** is shown in **Figure 1**, where the **SEM image** confirmed the formation of discrete, spherical microspheres with a smooth surface. This supports the effectiveness of the ionotropic gelation technique in producing uniform and well-formed particles.

The **in vitro drug release profiles**, provided in **Table 3**, demonstrate a sustained release pattern for all formulations over a 12-hour period. Among these, **SM2 exhibited the most desirable release behavior**, with **76.56**±2.80**% cumulative drug release at 12 hours**, followed by **SM9 (72.21**±2.51**%)** and **SM1 (71.53**±2.51**%)**. As seen in **Figure 2**, the release profile of SM2 is smooth, controlled, and free of burst release, which is ideal for maintaining therapeutic drug levels over an extended period.

To elucidate the release mechanism, the dissolution data of SM2 were analyzed using different kinetic models as shown in **Table 4**. The drug release followed **first-order kinetics** with the highest **correlation coefficient (R^2 = 0.9902)**, suggesting that the drug release rate is dependent on the remaining drug concentration in the microspheres. The **Higuchi model (R^2 = 0.9885)** indicates **diffusion-controlled release**, and the **Korsmeyer-Peppas model (R^2 = 0.9724)** suggests **non-Fickian (anomalous) transport**, which involves a combination of **diffusion and polymer relaxation/swelling mechanisms**. Graphical representations of these models are illustrated in **Figures 3 to 6**, supporting the kinetic model findings.

Table 2: Percent buoyancy, entrapment efficiency and yield of floating microspheres

Batch code	Buoyancy (%)	Drug Entrapment (%)	Yield (%)
SM1	82.01±03.25	58.25±2.11	63.28±2.33
SM2	**80.12±3.36**	**72.25±2.65**	**76.65±2.25**
SM3	73.21±3.11	68.27±2.58	74.45±2.14
SM4	83.41±3.36	62.53±2.58	68.27±2.25
SM5	75.17±3.14	56.27±2.74	70.27±2.36
SM6	76.29±3.22	58.74±2.36	73.29±2.33
SM7	76.41±3.15	55.57±2.25	70.12±2.74
SM8	71.32±3.33	66.28±2.41	69.98±2.33
SM9	74.42±3.30	70.49±2.36	73.22±2.74

All values are represented as mean±SD (n=3)

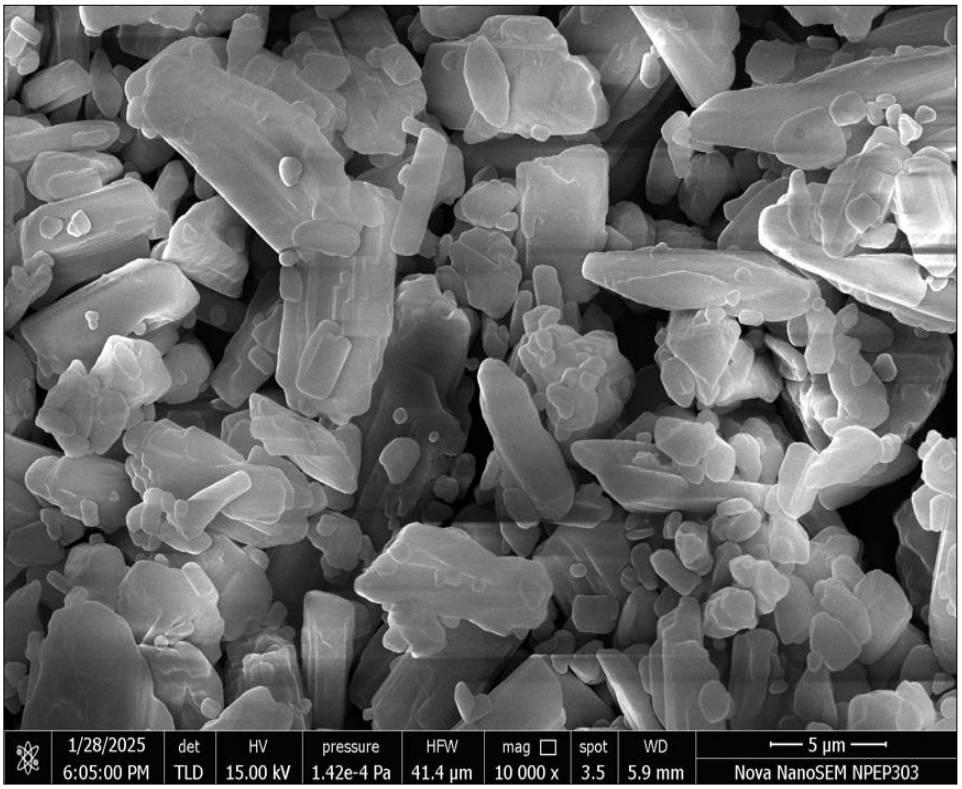

Figure 1: SEM image of optimized formulation SM2

Table 3: *In vitro* drug release study of Sitagliptin Microspheres

Time (h)	Cumulative % drug released								
	SM1	**SM2**	**SM3**	**SM4**	**SM5**	**SM6**	**SM7**	**SM8**	**SM9**
1	4.31±0.02	3.28±0.05	3.16±0.03	4.28±0.08	4.22±0.06	3.17±0.03	4.12±0.07	4.44±0.06	4.72±0.07
2	8.19±0.04	9.62±0.08	8.82±0.08	9.23±0.07	10.31±0.08	7.28±0.05	7.94±0.06	7.82±0.05	7.91±0.06
3	16.45±0.15	18.35±1.02	17.11±1.02	18.14±1.01	18.53±1.02	17.15±1.05	18.86±1.02	14.81±1.04	15.29±1.06
4	28.32±0.82	31.44±1.34	28.12±1.024	29.15±1.30	31.72±1.23	32.32±1.21	31.24±1.31	25.42±1.22	21.34±1.15
5	36.44±1.61	38.25±1.25	35.80±1.22	36.20±1.32	37.41±1.54	39.22±1.25	40.21±1.65	33.21±1.54	31.21±1.24
6	43.21±1.25	42.91±1.22	39.24±1.54	41.22±1.57	42.21±1.54	44.12±1.65	45.21±1.57	38.18±1.25	35.21±1.63
7	54.52±2.31	53.24±2.54	48.11±2.15	51.91±2.32	49.51±2.41	51.52±2.15	48.92±2.34	46.42±2.51	48.42±2.32
8	59.54±2.32	57.75±2.51	52.32±2.14	55.23±2.32	53.32±2.14	52.54±2.35	50.41±2.14	49.45±2.13	53.21±2.32
9	63.81±2.51	61.42±2.54	56.11±2.65	58.41±2.41	55.14±2.34	57.41±2.12	58.41±2.27	57.12±2.45	58.14±2.34
10	65.32±2.33	64.84±2.34	62.23±2.41	62.35±2.37	60.31±2.54	61.13±2.61	64.23±2.67	62.33±2.54	66.32±2.57
11	68.61±2.36	69.98±2.48	63.41±2.54	65.41±2.71	64.12±2.67	65.21±2.58	68.12±2.49	67.14±2.54	68.41±2.61
12	71.53±2.51	76.56±2.80	65.62±2.16	68.13±2.47	67.34±2.42	68.12±2.61	70.11±2.59	69.32±2.61	72.21±2.51

All values are represented as mean±SD (n=3)

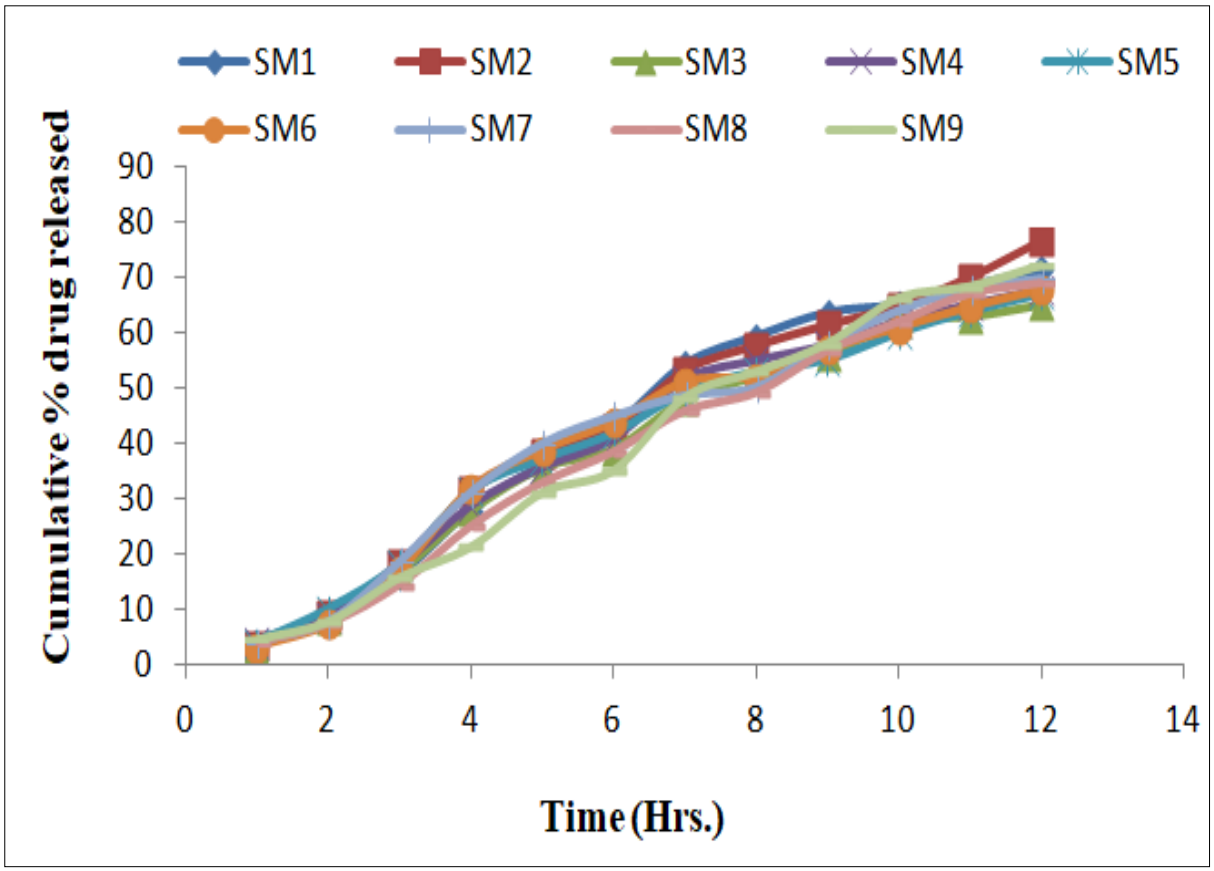

Figure 2: Cumulative percent drug release of floating microspheres

Table 4: Comparison of different dissolution kinetics models of the optimized formulation SM2

Formulation code	Kinetic models			
	Zero order release (R^2)	First order release (R^2)	Higuchi (R^2)	Korsemeyer Peppas (R^2)
SM2	0.9735	0.9902	0.9885	0.9724

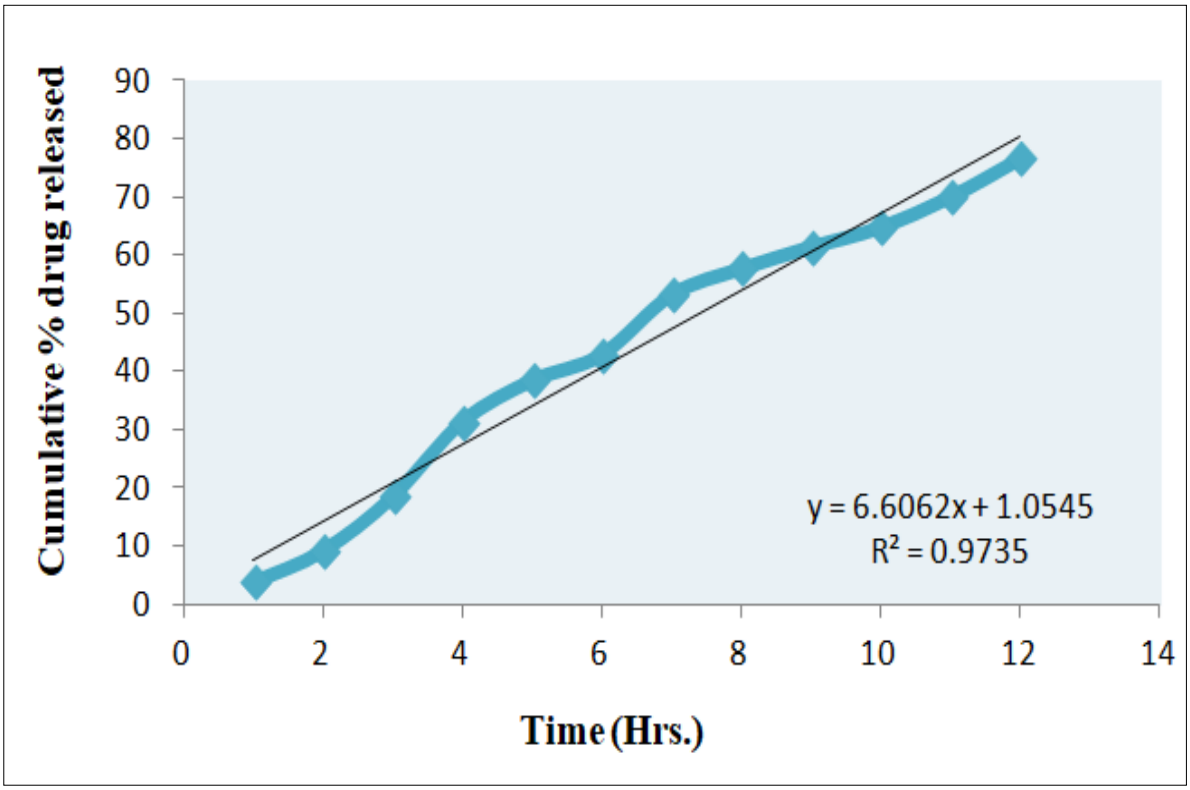

Figure 3: Zero order release model of formulation (SM2)

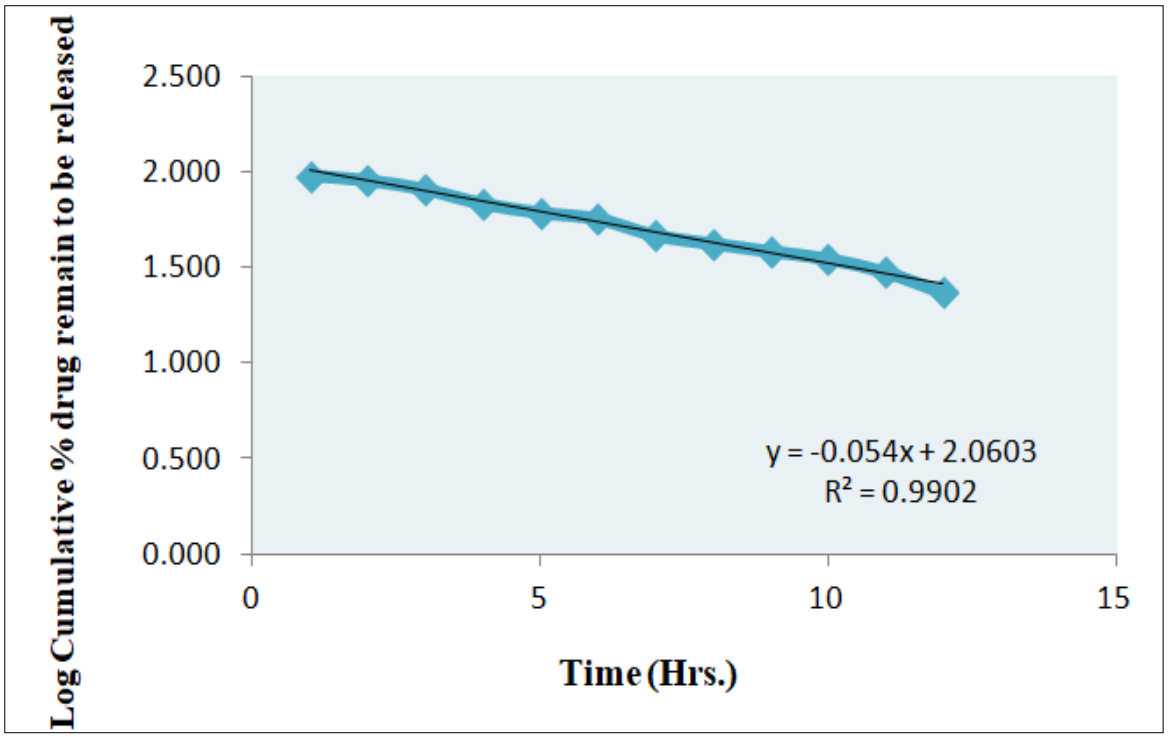

Figure 4: First order release model of formulation (SM2)

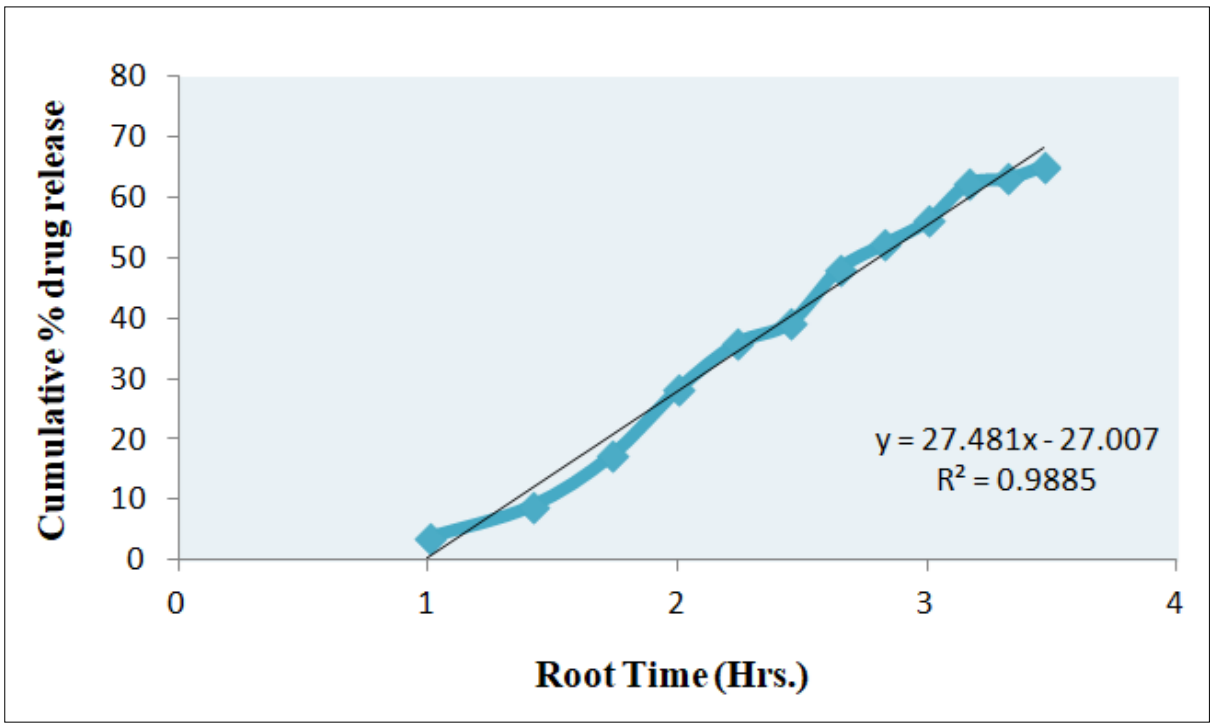

Figure 5: Higuchi model of formulation (SM2)

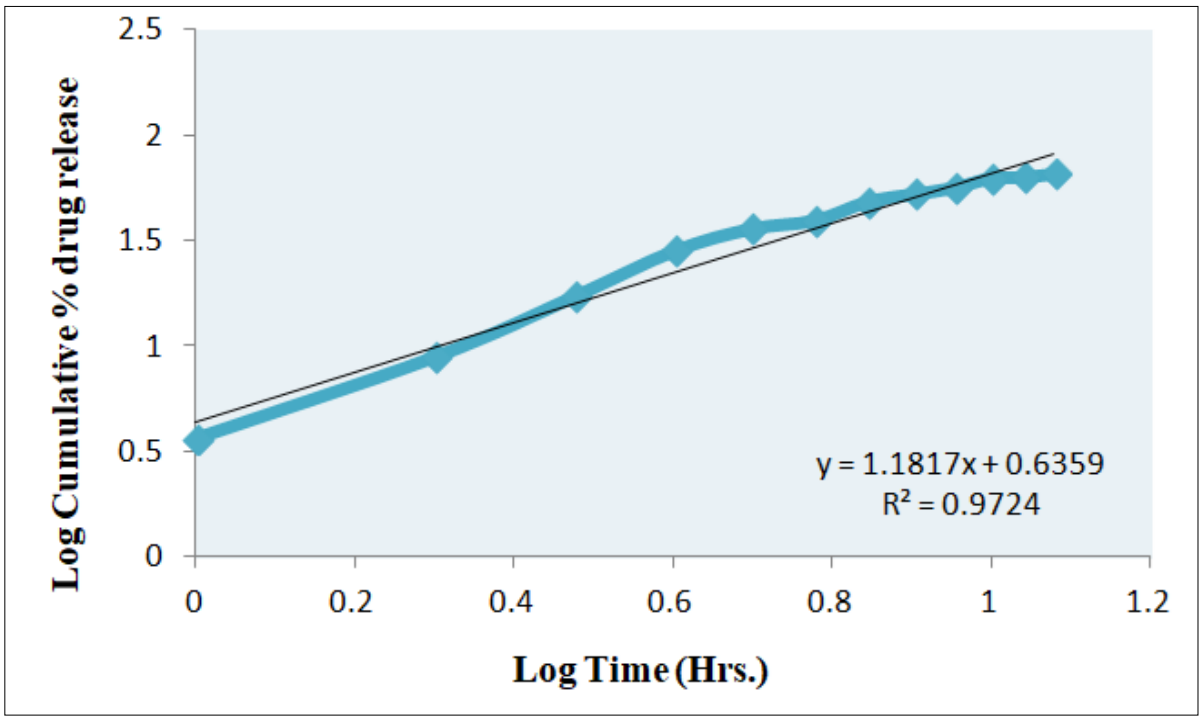

Figure 6: Korsemeyer Peppas model of formulation (SM2)

4. CONCLUSION

The study successfully developed **floating sustained-release microspheres of Sitagliptin** using ionotropic gelation with sodium alginate and chitosan. Among all batches, **formulation SM2** showed optimal performance with **high entrapment efficiency (72.25±2.65%), good buoyancy (80.12±3.36%),** and **sustained drug release (76.56±2.80% over 12 hours).** SEM confirmed spherical morphology, and kinetic analysis revealed **first-order, diffusion-controlled, and non-Fickian release.** SM2 is a promising candidate for improving the **oral delivery and therapeutic efficacy** of Sitagliptin in **type 2 diabetes**.

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