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FORMULATION AND CHARACTERIZATION OF FlOATING MICROSPHERES OF LANSOPRAZOLE

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Abstract

Context: To increase the duration Lansoprazole spends in the stomach, a continuous release mechanism was developed.

Objective: The influence of varied concentrations of different polymers on the creation of floating microspheres using the ionotropic gelation process.

Result: Microspheres were found to be spherical in form, with a mean diameter of 456.8m, according to morphological analysis. The production of Lansoprazole loaded Microspheres was achieved through the use of appropriate experimental conditions, with the F6 batch being identified as the Optimized formulation, with a high entrapment efficiency of 86.3 percent (w/w) and a high percent cumulative drug release of 92.24 percent 24th hr, indicating that Lansoprazole loaded Microspheres have the potential for prolonged drug release. After three months of testing at 4 + 1^{o}C and room temperature, the formulations demonstrate that they degrade faster at high temperatures. The Microsphere's optimal storage temperature, according to the findings, is a cool place.

Keywords: Floating microspheres, Lansoprazole, Ionotropic gelation method.

Introduction

Because of its potential advantages, such as tablet delivery mechanism, patient compliance, convenience, and cost effectiveness, oral drug administration is the most recommended route of drug delivery for pharmaceuticals, including a variety of diseases that have been effectively treated. Medication solubility, mucosal permeability, and gastrointestinal tract environment stability are all factors that influence oral drug absorption. Understanding the physicochemical, biochemical, metabolic, and biological obstacles that restrict total medication bioavailability employing various pharmaceutical technologies and drug delivery methods has been the focus of efforts to overcome these constraints (1, 2). To keep the pace of global

breakthroughs going, new drug delivery technologies are transforming medication research, development, and creation of R&D oriented pharmaceutical enterprises. In this regard, novel drug delivery systems (NDDS) offer numerous advantages, including improved therapeutic effect by increasing the efficacy and duration of drug activity, increased patient compliance by reducing dosing frequency, and improved site specific delivery to reduce unwanted side effects(3)

Gastro-retentive dosage forms are designed to be retained in the gastric region for prolonged time and release entrapped drug and thereby enable sustained and prolonged input of the drug to the upper part of the GIT thus ensuring its optimal bioavailability. They not only prolong the dosing intervals, but also increase the patient compliance beyond the level of existing controlled release dosage forms. Various approaches have been designed to improve period of retainment of oral dosage form in the stomach viz. floating system, swelling and expanding system, bio-adhesive system, high density system and other delayed gastric devices (4-8).

Because floating medication delivery systems have a lower bulk density than gastric fluids, they stay buoyant in the stomach for longer periods of time without influencing gastric emptying rate. The medicine is released slowly and at the desired rate from the system while it is floating on the gastric contents. As a result, the stomach retention period was increased, and the fluctuations in plasma drug concentration were better controlled. Floating microspheres are non-effervescent drug delivery devices that are gastro-retentive. Floating microspheres are also known as hollow microspheres, microballoons, or floating microparticles. In a strict sense, floating microspheres are spherical empty particles without a core. These are free-flowing particles that range in size from 1 to 1000 micrometres. They float on gastric fluid that has a density less than one. As a result of this trait, stomach transit is slowed. The drug is slowly delivered at the desired rate, leading in enhanced stomach retention and lower volatility in plasma drug concentration (9-12).

Lansoprazole is a proton pump inhibitor that is both selective and irreversible. Lansoprazole has an oral bioavailability of 80-90 percent, according to studies. Because food lowers Lansoprazole absorption (both C_{max} and AUC are lowered by 50-70 percent), patients should be instructed to take it before meals. Lansoprazole has a half-life of 2 hours or less. Lansoprazole has a peak plasma concentration (C_{max}) of roughly 1.7 hours after oral dosage, making it a good option for FDDS to extend gastro retention (13, 14).

Material and Methods

Metrochem API Pvt. Ltd., Hyderabad, India, generously provided Lansoprazole as a gift sample. Nice Chemicals provided the sodium alginate, guar gum, and xanthan gum (Cochin, Kerala, India). All of the other reagents and substances used in this experiment were of analytical quality.

Preparation of Floating Microspheres

For the manufacture of microspheres, the ionotropic gelation process was chosen. Individually, xanthan gum and guar gum were dissolved in distilled water and allowed to swell for many hours (Solution1). The medication was disseminated when sodium alginate was dissolved in distilled water (solution2). The 1 and 2 solutions were combined, sodium bicarbonate was added, and the mixture was maintained at room temperature with a constant speed on a magnetic stirrer. With a 21 gauze needle, the bubble-free dispersion was placed into several cross linking agent solutions. The microspheres were supposed to solidify for 15 minutes in the solution. The microspheres were filtered and dried at ambient temperature first, then in a hot air oven at 35 degrees Celsius for around 30 minutes. Microspheres were kept in glass vials that were firmly closed (15, 16).

Evaluation of Floating microspheres of Lansoprazole

Particle size and surface morphology analysis

An optical microscope was used to examine the particle size of the prepared Microspheres. Before being measured, the Microspheres were suspended in deionized water and sonicated for 1 minute with an ultra-sound instrument.

Surface and shape analysis by Field Emission Scanning Electron Microscopy

Field Emission Scanning Electron Microscopy at 10 kV was used to examine the shape and surface features of Microspheres. Excess samples were removed and coated with gold for 20 seconds after being placed on an aluminium stub with adhesive tape. The metal stub was then vacuum-sprayed for 20 minutes in an E-1010 ion sputter. The materials were evaluated using a Field Emission Scanning Electron Microscope after 20 minutes.

Differential Scanning Calorimetry

DSC is a thermal analytical technique in which the difference in the amount of heat required to raise the temperature of a sample and a reference is measured as a function of temperature. Throughout the experiment, the sample and reference are kept at nearly the same temperature. Lansoprazole (5 mg) was heated in sealed aluminium pans at a rate of 10oC/min under nitrogen environment (60 ml/min) from 30°C to 300°C. As a reference, an empty aluminium pan was used.

Entrapment Efficiency

The concentration of the integrated material (such as active chemicals, medicines, etc.) detected in the formulation above the original concentration utilized to manufacture the formulation is characterised by the Entrapment Efficiency (EE percent). The Microspheres' entrapment effectiveness was measured spectrophotometrically. Lansoprazole Microspheres (10 mg) were dissolved in 10 ml of Methanol and stored overnight. 1 ml of the supernatant was collected and diluted to 10 ml with Phosphate Buffer (pH 7.4) before being measured at 223 nm with a UV-Visible spectrophotometer. Eq.1 was used to compute the percent entrapment effectiveness of the Microspheres based on the absorbance.

$$\%\ \textbf{Entrapment efficiency} = \frac{\textbf{observed drug content}}{\textbf{initial drug content}} \times 100$$

Eq.1

In vitro Buoyancy studies

Floating lag time and total floating duration were used to estimate in vitro buoyancy. In a 100ml beaker containing 0.1N HCl, the microspheres were inserted. The time it took the microspheres to rise to the surface and float was measured as floating lag time (FLT), and the total amount of time they stayed afloat on the dissolving medium was measured as Total Floating Time (TFT) (17)

$$\%\text{Buoyancy} = Qf/(Qf+Qs) \times 100$$

Eq. 2

Where Qf and Qs are the weight of the floating and settled microspheres respectively.

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

The release pattern of the medication from microsphere formulations generated by the ionotropic gelation technique was studied in vitro. The Microspheres pill was placed in the dialysis bag, which had already been soaked and rinsed multiple times with distilled water. This was placed in 100ml of phosphate buffer solution (pH 6.8) and held at 37oC with continual agitation on a magnetic stirrer. At each interval, the entire sample was extracted and the same values were replaced with buffer. The samples were then spectrophotometrically analyzed between 200 and 400 nanometers using medium as a blank.

Drug release kinetics from Microspheres

The process through which a drug exits a drug product and is subjected to absorption, distribution, metabolism, and excretion (ADME) before becoming available for pharmacological action is known as drug release. It is recognised as a critical component in the development of pharmaceuticals. It can be used as a proxy for bioequivalence testing under specific circumstances. The use of a generic equation to quantitatively translate the dissolution curve in the function of some other parameters linked to pharmaceutical dosage forms simplifies the quantitative interpretation of the result obtained in the dissolution assay. In other circumstances, such as zero order kinetics, that equation can be inferred from a theoretical understanding of the process (18).

The following is the method of investigation used to look into the Kinetics of Release from Controlled Release:

• Statistical approach [two-way analysis of variance, or ANOVA].

• Methods that are model dependant [zero order, first order, Higuchi, and Korsmeyer-Peppas models].

Results and discussion

Particle size and surface morphology analysis

Optical microscopy was used to determine the size of Lansoprazole particles. The mean particle size of optimized microspheres was found to be 456.8 micrometers.

Surface analysis and shape by Field Emission Scanning Electron Microscopy

The Microspheres surface morphology was studied using FE-SEM, as shown in Fig. 1 and Fig. 2, indicating that they are spherical in form. The Microspheres have a rough and porous surface.

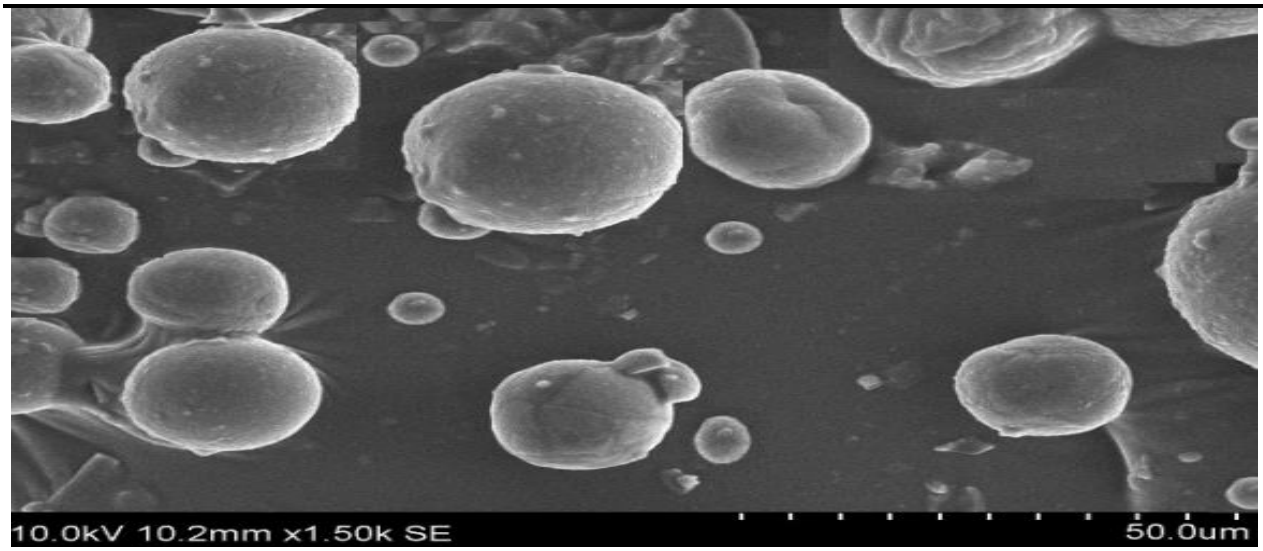

Figure 1 : FE-SEM of Lansoprazole loaded Microspheres

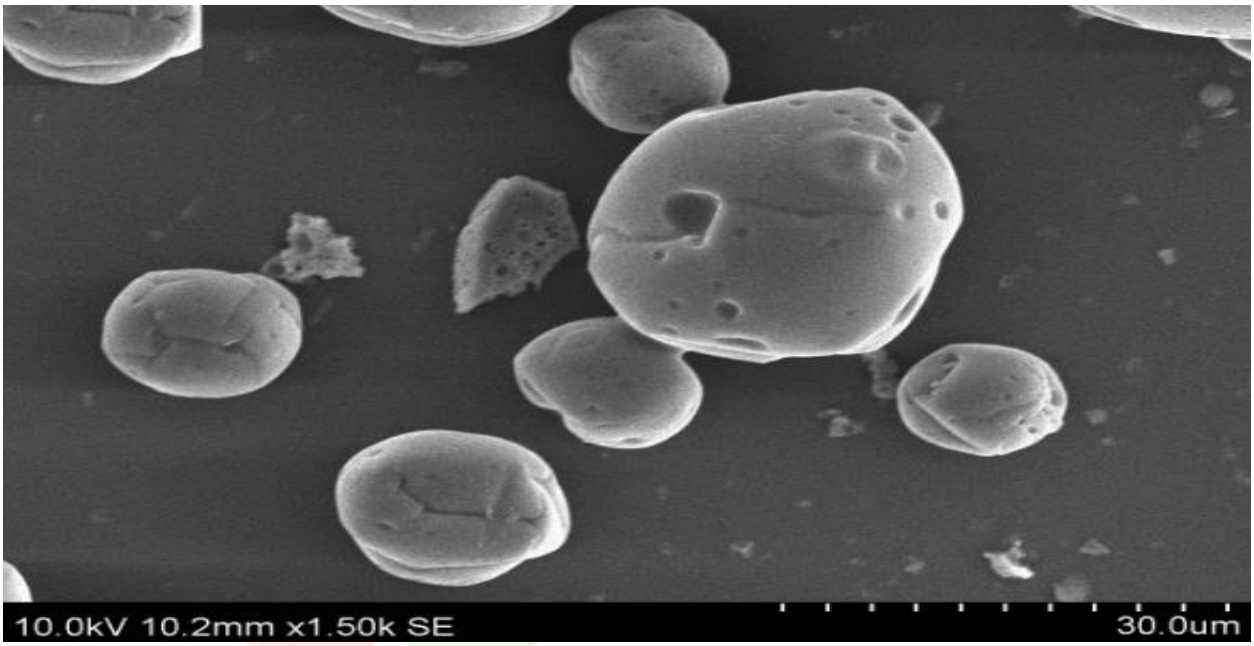

Figure 2: FE-SEM of Lansoprazole loaded Microspheres

Differential Scanning Calorimetry (DSC)

Figure 3 presents the DSC thermogram of Lansoprazole which shows an endothermic peak around 174.77^{0}C, which corresponds to its melting point range.

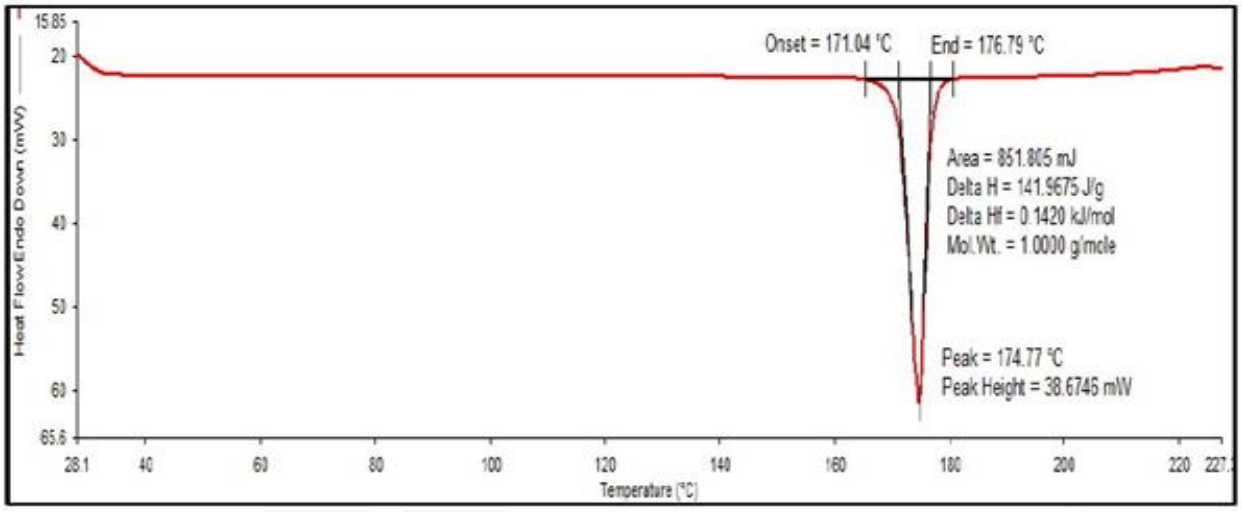

Figure 3: DSC Thermogram of Lansoprazole

Entrapment Efficiency

Microsphere drug entrapment effectiveness ranged from 74.23 % to 94.16 %. The entrapment efficiency of the medication rose as the concentration of Xanthan gum increased, according to the findings.

Batch Code	SA:GuarGum (X_1)	SA:Xanthan gum (X_2)
F_1	- (4:1)	- (4:1)
F_2	- (4:1)	0(4:3)
F_3	- (4:1)	+ (4:5)
F_4	0(4:3)	- (4:1)
F_5	0(4:3)	0(4:3)
F_6	**0(4:3)**	**+ (4:5)**
F_7	+ (4:5)	- (4:1)
F_8	+ (4:5)	0(4:3)
F_9	+(4:5)	+ (4:5)

***In vitro* Buoyancy studies**

Buoyancy percentage of nine batches are summarized in **Table 2**

Table 2 Buoyancy % of Floating Microspheres

Formulation code	Buoyancy %
F_1	69.25
F_2	82.45
F_3	78.45
F_4	72.98
F_5	80.32
F_6	**84.34**
F_7	74.52
F_8	81.56
F_9	71.23

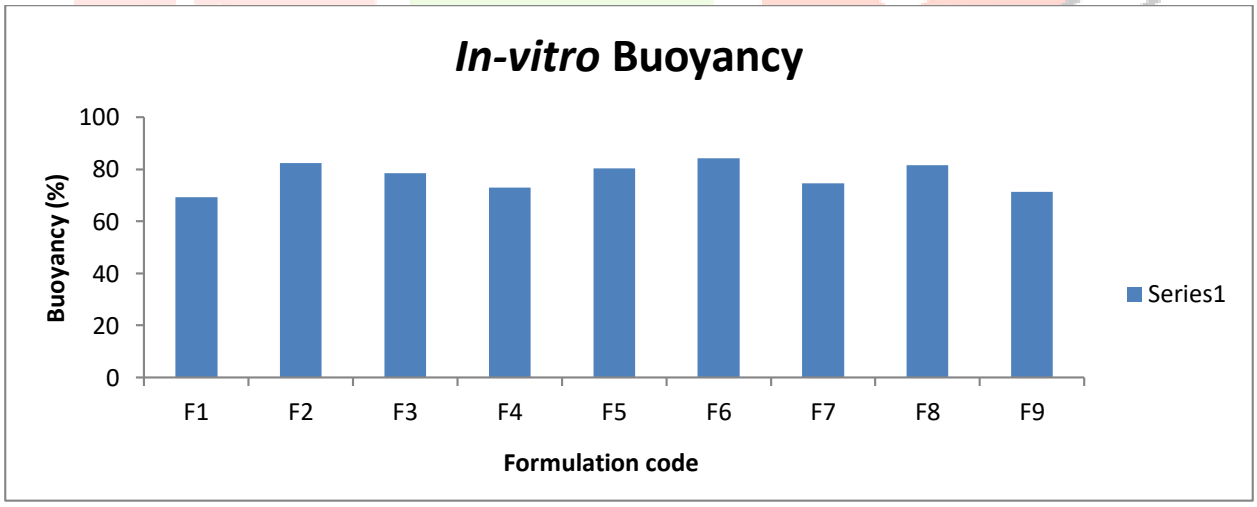

Figure 4: *In-vitro* Buoyancy of Microspheres

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

In-vitro Drug release study of nine formulations (F_1-F_9) is summarized in **Table 3.**

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	14.45± 0.66	12.26± 0.68	9.42±0. 97	11.30± 0.95	10.59± 0.95	**12.52± 0.95**	10.73± 0.71	10.78±. 80	11.74± 83
1	13.80± 0.50	19.80± 0.80	18.40± 0.65	17.52± 0.75	16.80± 0.65	**17.28± 0.51**	14.62± 1.89	16.15± 0.85	17.54± 0.79
2	29.95± 1.12	21.50± 0.63	25.72± 0.82	28.82± 1.31	27.95± 1.25	**25.88± 0.82**	29.05± 0.51	25.32± 0.69	21.55± 0.42
4	31.85± 0.81	39.91± 0.93	34.85± 0.65	32.45± 0.51	38.49± 0.96	**36.72± 1.15**	31.86± 0.68	36.15± 0.77	37.42± 0.77
6	49.48± 0.75	42.68± 0.95	47.95± 0.75	40.15± 0.46	44.59± 0.61	**44.92±. 91**	49.02± 0.72	45.92± 0.85	48.54± 0.29
8	52.71± 0.91	59.21± 0.79	53.95± 0.66	54.75± 0.95	50.75± 1.61	**55.59± 0.61**	50.76± 0.52	54.92± 0.71	53.91± 0.53
10	69.52± 0.35	61.95± 0.52	67.82± 0.45	65.81± 0.76	70.25± 0.85	**68.75± 0.31**	64.80± 0.12	62.75± 0.31	59.72± 0.54
12	72.95± 0.51	75.21± 0.85	79.25± 0.36	76.36± 0.58	84.81± 0.63	**77.81± 0.60**	73.67± 0.65	74.81± 0.96	64.71± 0.98
24	81.71± 0.56	83.33± 0.91	87.15± 1.23	89.65± 0.75	91.51± 0.71	**92.24± 1.24**	87.42± 1.58	82.65± 0.89	79.32± 0.78

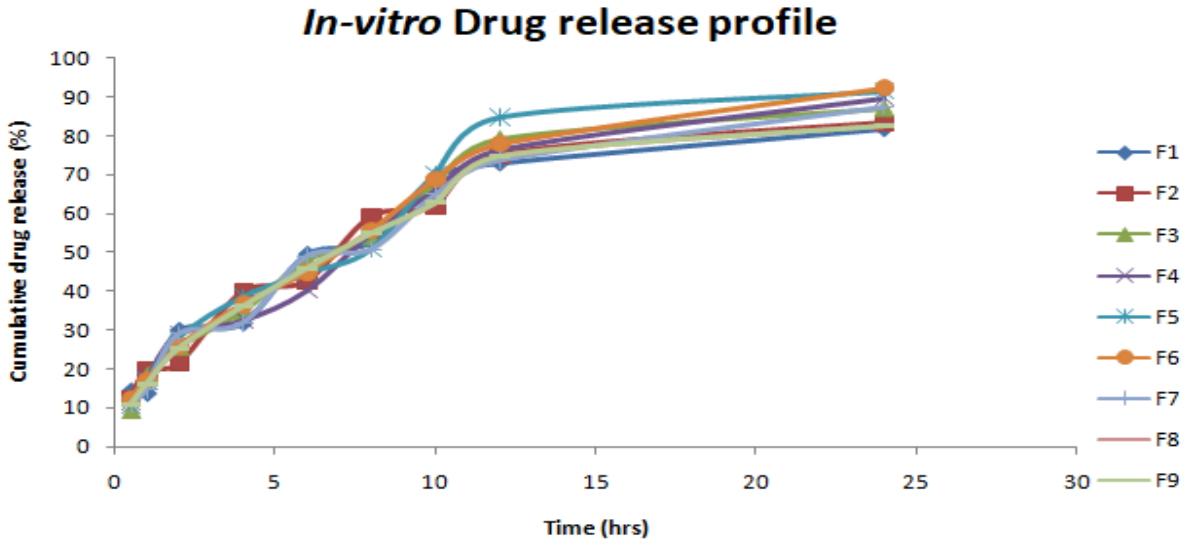

Figure 5: *In-vitro* drug release study

Kinetics of drug release

The data collected from in-vitro release of the final optimised batch was fitted into equations for the zero-order, first-order, Higuchi release model, and Korsmeyer-Peppas equation in order to explore the release mechanism of the present drug delivery system. The values of regression coefficient derived from several kinetics models are listed in Table 4.

Table 4: Regression coefficient (R^2) obtained from various kinetics models

Batch Code	Zero Order Kinetics	Higuchi Kinetics	Korsmeyer-Peppas Kinetics	N	First Order Kinetics
F_1	0.844	0.979	0.969	0.608	0.624
F_2	0.883	0.989	0.994	0.580	0.704
F_3	0.874	0.986	0.950	0.620	0.617
F_4	0.892	0.995	0.997	0.552	0.712
F_5	0.888	0.987	0.984	0.581	0.691
F_6	**0.899**	**0.985**	**0.988**	**0.743**	**0.683**
F_7	0.875	0.992	0.983	0.575	0.663
F_8	0.860	0.986	0.953	0.606	0.609
F_9	0.887	0.994	0.994	0.558	0.706

The values of the obtained regression coefficients were used to interpret the data. The regression coefficient values of the optimised formulation (F_6) for Zero order (R^2= 0.899) as shown in Fig. 6, Higuchi's model (R^2= 0.985) as shown in Fig. 7, Peppass model (R^2= 0.988) and with a value of n = 0.734 as shown in Fig. 8, and First order (R^2 = 0.683) as shown in Fig. 9 The optimal formulation of Micrsospheres follows the Korsmeyer-Peppas model with a release exponent value of n = 0.743, based on the best fit with the highest correlation (R^2) value. The release mechanism is Non-fickian diffusion based on the size of the release exponent n.

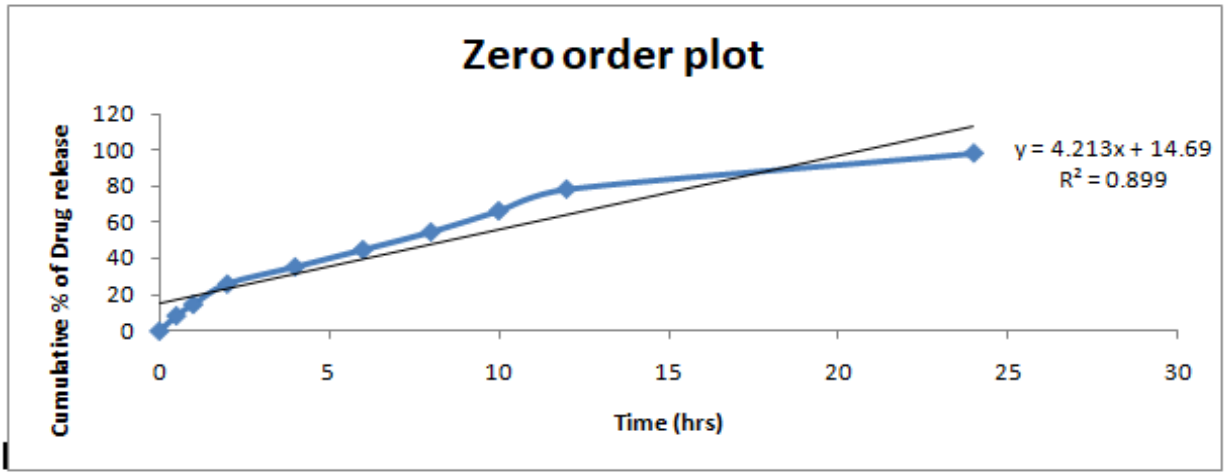

Figure 6 : Zero order plot of the optimized formulation (F_6)

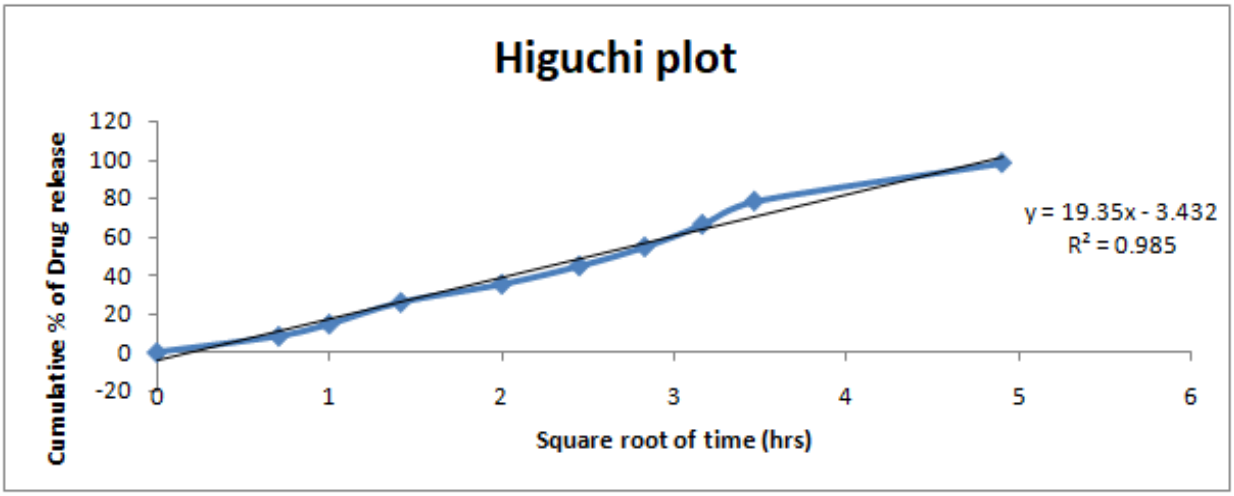

Figure 7: Higuchi plot of the optimized formulation (F_6)

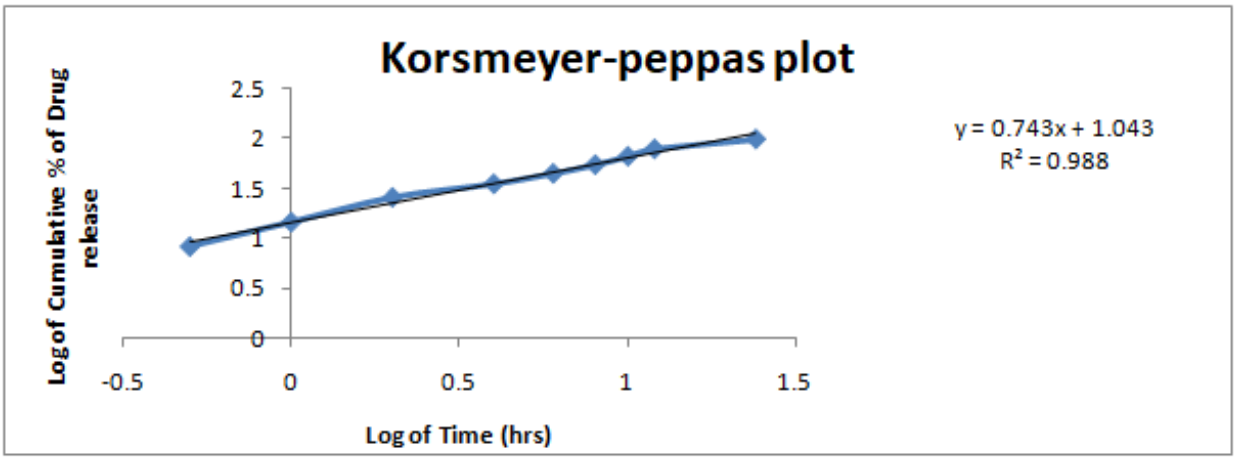

Figure 8 : Korsmeyers-peppas plot of the optimized formulation(F_6)

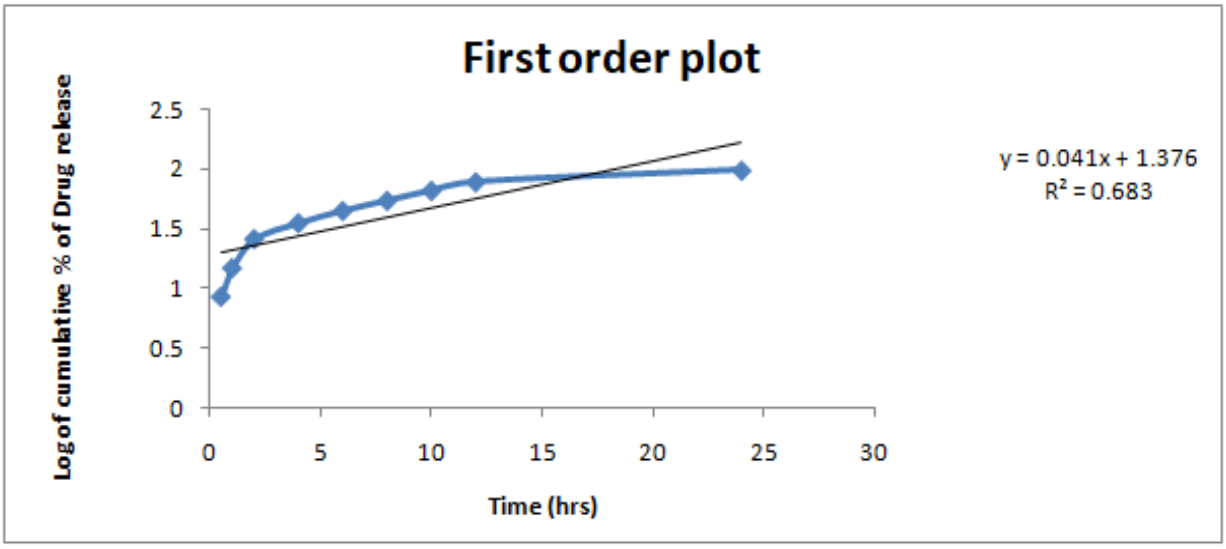

Figure 9: First order plot of the optimized formulation (F_6)

Conclusion

The design and development of a gastro-retentive drug delivery system based on a non-effervescent method proved successful. Lansoprazole floating microspheres were created and optimized in this work. In simulated GI fluids, the microspheres were discrete, spherical with a core hollow hole, and demonstrated sustained drug release patterns. The concentration of Polymers influenced drug entrapment efficiency, drug release, and microsphere particle size. At the 24th hour, the percent cumulative drug release was found to be 92.24 %.

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