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Formulation Development and In-vitro Evaluation of Sitagliptin Floating Tablets

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Abstract

The present research work done with an objective of preparation and evaluation of floating tablets of Sitagliptin drug with hydroxypropylene methyl cellulose (HPMC), Xanthum Gum and Guar gum polymers. Floating tablets were based on effervescent approach using sodium bicarbonate a gas releasing agent. Direct compression method was used in present study for preparation of tablets. Effect of polymers was evaluated by studying swelling properties and floating time. In-vitro drug release profile indicates that sustained nature increased by increasing the concentration of polymer. The formulation containing Guar gum with 40% concentration is optimized as it showed drug release up to 12hrs. Optimized formulation with 35mg of floating agent per tablet showed desired floating lag time.

Keywords: Floating tablets, Xanthum gum, Guar gum, Sitagliptin, HPMC, Floating lag time.

Introduction

All the pharmaceutical products designed for systemic delivery through the oral route of administration, different type of deliveries such as Sustained Release SR, Controlled Release CR, & Immediate Release IR and the design of dosage form (SD / liquid), developed within the intrinsic characteristics of GI physiology [1].

The successful development of Oral drug delivery system ODDS consists of basic understanding like:

(i) Pharmaco kinetics & dynamics & Physicochemical characteristics of the drug.

(ii) The anatomic & physiologic characteristics of the GIT.

(iii) mode of the dosage form to be designed.

Difficulties conventional oral controlled dosage [2]

1. The short gastric retention time (GRT).

2. Unpredictable gastric emptying time (GET).

Gastro retentive drug delivery system GRDDS

Complete information about GI dynamics like as gastric emptying, small intestine transit, colonic transit, etc. is the key for the designing of oral controlled release dosage forms. The rate & extent of drug absorption from different sites of GI tract and factors that govern the absorption further assist the design of dosage form.

GRDDS

Different types of methods were used to enhance the retention of orally administered forms into the stomach: Floating method, Extending method, Bioadhesive method, Modified shape method, High-density method and other delayed gastric-emptying devices.

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Table 1: Formulations of Sitagliptin floating tablets.

Ingredients (mg)	S1	S2	S3	S4	S5	S6	S7	S8	S9
SITAGLIPTIN	100	100	100	100	100	100	100	100	100
HPMC	105	122.5	140	--	--	--	--	--	--
XANTHUM GUM	--	--	--	70	87.5	140	--	--	--
GUAR GUM	--	--	--	--	--	--	70	87.5	140
MCC	42	24.5	7	77	59.5	7	77	59.5	7
$NaHCo_3$	35	35	35	35	35	35	35	35	35
Citric acid	12	12	12	12	12	12	12	12	12
Mg. Stearate	6	6	6	6	6	6	6	6	6
Total Weight	**350**	**350**	**350**	**350**	**350**	**350**	**350**	**350**	**350**

Advantages of Floating drug delivery systems FDDS [3,4]: Floating technique was modified technology with gastric retentive behavior and it contains no. of advantages.

These advantages include:

1. improved bioavailability.
2. SR reduced frequency of dosing
3. Site specific therapy for GIT.
4. Minimize adverse activity at the colon.
5. Reduced variations of drug conc.

Disadvantages of FDDS:

1. The drugs that are unstable in the acidic environment of the stomach are not suitable candidates to be incorporated in the systems.

2. These are requiring a great concentration of fluid in the stomach for drug delivery to float and work efficiency.

3. Not appropriate for drugs that have solubility / stability problem in GIT.

Types of FDDS [4]: Based on the method of buoyancy, two different technologies have been utilized in development of FDDS which are:

A. Effervescent system:

It was further separated into 2 types.

I. Gas liberating systems

II. Volatile Liquid/Vacuum Containing Systems.

B. Non-Effervescent system: [5]

The various types of this system are as:

- Single Unit Floating dosage system
- Multiple Unit Floating dosage system

Materials and Methods

Materials

Sitagliptin was used as active agent and it is gifted sample from Chandra labs, Hyderabad. Polymers like HPMC, Guar gum, Xanthum gum and floating agent Sodium bicarbonate, Citric acid, filler like Micro crystaline cellulose were laboratory grade reagents.

Methodology

Preparation of calibration curve for Sitagliptin in 0.1N HCL: Prepare 2.5, 5, 7.5, 10, 12.5 and 15 µg/mL concentrations of Sitagliptin solution in 0.1N HCL and note absorbance against blank at 288nm using UV absorption spectrophotometer.

Drug and Excipients compatibility studies using FTIR: In this FTIR the drug functional groups were identified and Compatibility was observed of these excipients with Sitagliptin.

Sitagliptin floating tablets Formulation by direct compression method

Insert **(**Table 1)

Pre-formulation studies: Pre formulation studies include Description, solubility, melting point of drug and flow properties of formulation blends before punching. Flow properties like Bulk density, Tapped density, Angle of repose, Compressibility index and Hausner's ratio were studied.

Post compression parameters: Prepared tablet formulations were studied for Thickness, Hardness, Friability, weight variation, swelling index, Buoyancy studies and In-vitro drug release studies.

Kinetic Analysis of *in-Vitro* Release Rates of Floating Tablets of Sitagliptin [6]**:** The results of *in vitro* release profile obtained for all the formulations were plotted in modes of data treatment as follows,

1. Zero order kinetic model
2. 1^{st} order kinetic model
3. Higuchi's model
4. Korsmeyer equation / Peppa's model [7,8]

Results and Discussion

Pre formulation results

Description: These tests were performed the results were illustrated in the following table and the results were found as per specifications table 2.

Solubility: These tests were performed and the results are illustrated in the table 3.

Melting Point: This test is performed the result was as per specification only and result illustrated in the following table 4.

Calibration curve of Sitagliptin in 0.1N HCL

Table 5, Figure 1

Fourier transformer infrared spectroscopy FTIR

By correlating Sitagliptin peaks of pure drug spectrum with physical- mixtures of the optimized formulation it was found that the drug is compatible with the formulation components (Figures 2 and 3).

Evaluation of pre-compression parameters for Sitagliptin floating formulations

Table 6

Post compression parameters evaluation for floating tablets

Table 7 and 8

In vitro dissolution studies for floating tablets in 0.1N HCL

For gastro retentive formulations generally 0.1N HCL was used as dissolution medium and for present formulations 900ml 0.1N HCL, USP Type 2 paddle apparatus, and 5ml samples were withdrawn for every time point Table 9 and Figures 4,5 and 6.

Drug Release kinetics

Table 10

Summary and Conclusion

Gastroretentive drug delivery is an approach to prolong gastric residence time thereby targeting site-specific drug release in the upper gastrointestinal tract for local or systemic effects. Gastroretentive dosage forms remain in the gastric region for longer period and hence significantly prolong the gastric retention time of drugs.

Gastro retentive dosage form by Guar gum was prepared and to develop a floating tablets of Sitagliptin that could retain in the stomach for longer periods of time delivering the drug to the site of action, i.e., in stomach.

Among those anti-diabetic medications Sitagliptin was more acceptable. Sitagliptin Phosphate is a Dipeptidyl Peptidase-4 (DPP-4) Inhibitor. Sitagliptin competitively inhibits the enzyme dipeptidyl peptidase 4 (DPP-4). This enzyme breaks down the incretins GLP-1 & GIP, GI hormones released in response to a meal. By preventing GLP-1 & GIP inactivation, they are able to increase the secretion of insulin and suppress the release of glucagon by the pancreas. This drives blood glucose levels towards normal.

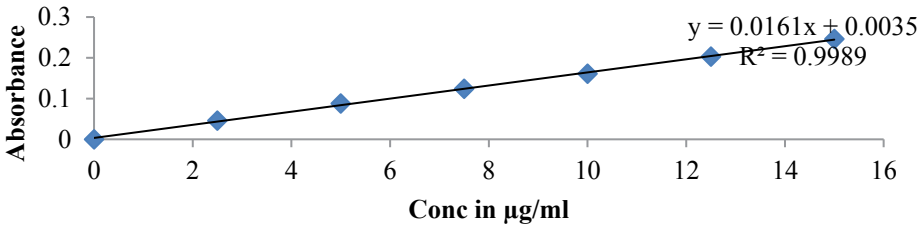

Figure 1: Calibration curve plot of Sitagliptin.

Table 2: Table showing the description of Sitagliptin (API).

Test	Description
Colour	White to off white powder
Odour	Free of odour

Table 3: Table showing the Solubility of Sitagliptin (API) in various solvents.

Solvents	Solubility
Water	soluble
Ethanol	Soluble
Methanol	Slightly Soluble
Acetone	Soluble

Table 4: Table showing the melting point of API's.

Material	Melting Point
Sitagliptin	216-219^{0}c

Table 5: Calibration Curve Data of Sitagliptin.

Concentration (µg /ml)	Absorbance
0	0
2.5	0.046
5	0.088
7.5	0.124
10	0.161
12.5	0.203
15	0.246

Table 6: Pre-compression parameters (S1-S9).

Formulation code	Bulk density (g/cc)	Tapped density (g/cc)	Carr's Index	Hausner Ratio	Angle of repose(θ)
S1	0.45±0.045	0.52 ± 0.09	15.60±0.2	1.15±0.02	28.06± 0.31
S2	0.45±0.045	0.50 ± 0.07	12.23±0.6	1.11±0.04	27.58± 0.15
S3	0.44±0.044	0.50 ± 0.09	12.58±0.8	1.13±0.08	28.44± 0.11
S4	0.45±0.045	0.52 ± 0.04	15.19±0.1	1.15±0.06	28.36± 0.13
S5	0.44±0.044	0.52± 0.01	15.48±0.6	1.18±0.08	28.52± 0.19
S6	0.45±0.045	0.51 ± 0.04	13.48±0.8	1.13±0.09	29.32± 0.19
S7	0.51±0.045	0.59 ± 0.04	14.48±0.8	1.15±0.09	29.69± 0.19
S8	0.45±0.045	0.50 ± 0.07	12.23±0.6	1.11±0.04	27.58± 0.15
S9	0.45±0.045	0.52 ± 0.04	15.19±0.1	1.15±0.06	28.36± 0.13

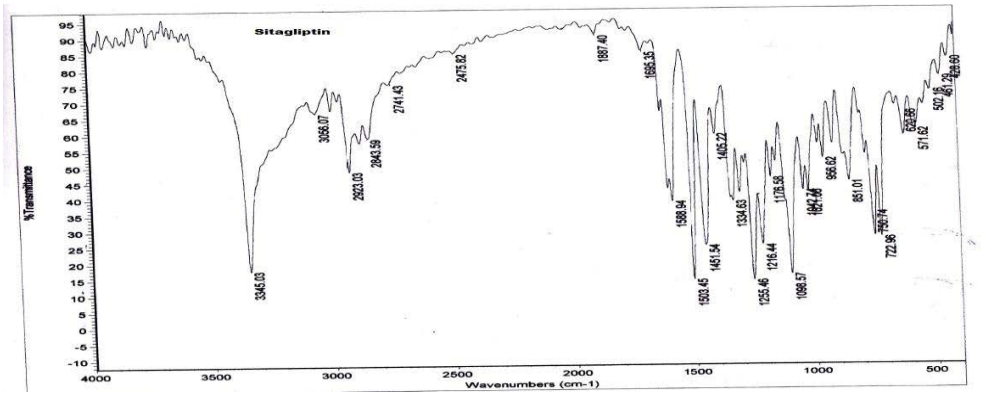

Figure 2: FTIR sprectra of drug Sitagliptin.

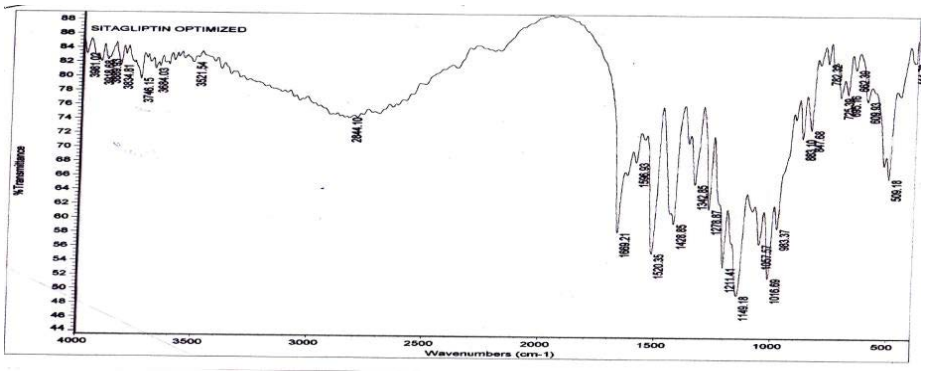

Figure 3: FTIR Spectra of optimized floating sitagliptin formulation blend.

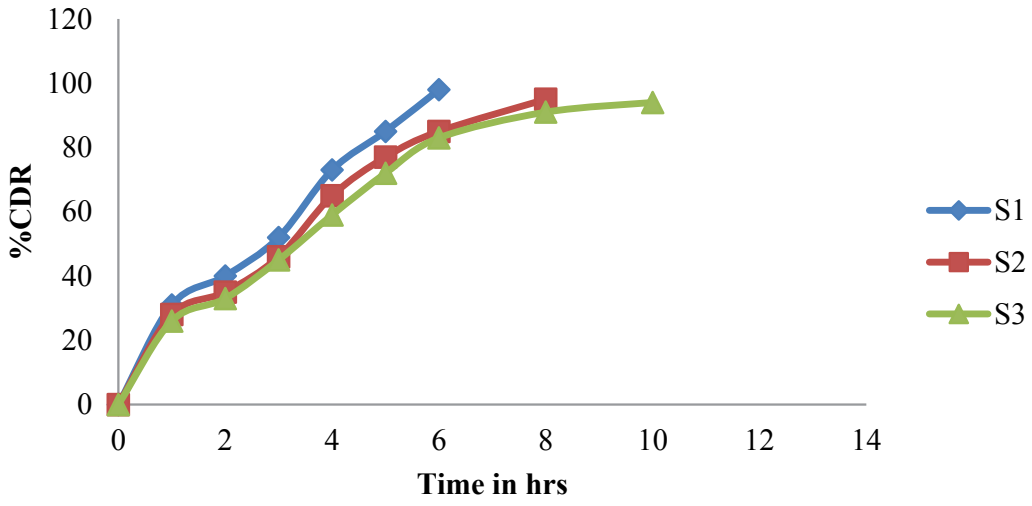

Figure 4: Dissoulation graph for S1 – S3.

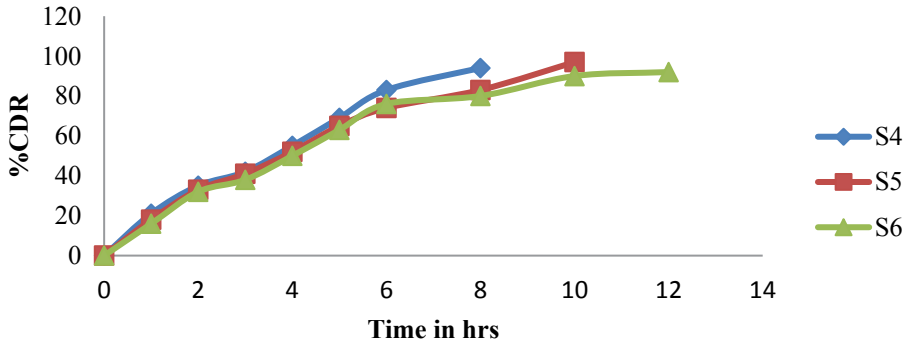

Figure 5: Dissolution graphs for S4-S6.

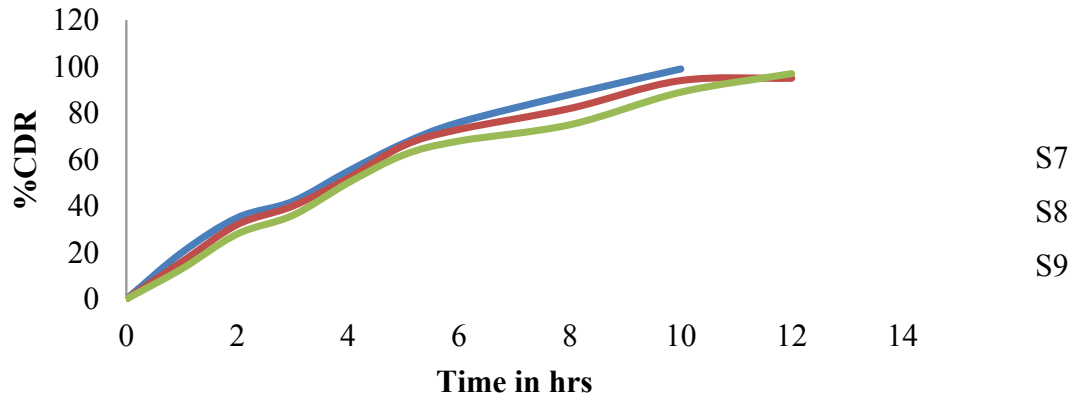

Figure 6: Dissolution graphs for S7-S9.

Table 7: Post compression parameters (S1-S9).

Formulation Code	Weight Variation (mg)	Thickness (mm)	Hardness (kg/cm²)	Friability (%)
S1	344±1.36	3.28±0.20	7.3±0.54	0.72±0.41
S2	348±2.02	3.33±0.22	7.5±0.75	0.37±0.42
S3	350±1.89	3.28±0.17	7.6±0.45	0.40±0.38
S4	347±1.99	3.16±0.05	7.9±0.25	0.46±0.36
S5	348±2.49	3.84±0.17	7.3 ±0.44	0.32±0.25
S6	347±1.99	3.92±0.25	7.6±0.31	0.30±0.17
S7	349±0.89	3.80±0.80	7.6±0.40	0.36±0.20
S8	350±1.88	3.82±0.20	7.5±0.55	0.31±0.25
S9	346±1.15	3.98±0.66	7.7±0.57	0.34±0.36

Table 8: Post compression parameters (S1-S9).

Formulation Code	Drug content (%)	Floating lag time	Swelling index (%)	Floating duration (hrs)
S1	98.78±0.24	46sec	32.12	6.3
S2	97.70±0.38	52sec	34.26	8.1
S3	99.51±0.32	59sec	36.01	9.2
S4	99.94±0.21	4min	34.95	8.3
S5	98.42±0.28	6min	37.23	10.1
S6	98.91±0.23	7min	38.18	11.0
S7	98.58±0.24	12sec	36.55	10.3
S8	99.26±0.44	28sec	37.75	11
S9	99.12±0.32	36sec	39.66	12

Table 9: Dissolution data of formulation S1-S9.

Time (hrs)	S1	S2	S3	S4	S5	S6	S7	S8	S9
1	31	28	26	21	18	16	20	16	13
2	40	35	33	35	33	32	35	32	28
3	52	46	45	42	41	38	42	40	36
4	73	65	59	55	52	50	55	52	50
5	85	77	72	69	65	63	67	66	62
6	98	85	83	83	74	76	76	73	68
8	-	95	91	94	83	80	88	82	75
10	-	-	94	-	97	90	99	94	89
12	-	-	-	-	-	92	-	95	97

Table 10: Kinetic values of S9 formulation.

	ZERO	FIRST	HIGUCHI	PEPPAS
	% CDR Vs T	Log % Remain Vs T	%CDR Vs √T	Log C Vs Log T
Slope	7.971202304	-0.11465774	30.35961017	1.308499573
Intercept	11.14686825	2.115093439	-9.78941327	0.761137851
Correlation	0.972099715	-0.96315767	0.985702545	0.846467921
R 2	0.944977857	0.927672697	0.971609507	0.716507941

Formulations prepared using direct compression method. The prepared tablets of all the formulations were evaluated for physical characters tablet thickness, hardness and friability, swelling index, floating lag time, total floating time, drug content and *in-vitro* drug release.

S9 formulation with Guar gum as polymer showed highest drug release for 12 hrs and good buoyancy results. Optimized formulation dissolution data is studied for kinetic release studies and optimized S9 formulation follows Higuchi model.

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