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Formulation and evaluation of Repaglinide biphasic mini tablets

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ABSTRACT

Repaglinide is an anti-diabetic drug used extensively in the treatment of diabetes type II. The present study was carried out to formulate and evaluate biphasic floating mini tablets of Repaglinide. These mini tablets were encapsulated in a capsule. Immediate release mini tablet (IRMT) were manufactured by direct compression using various superdisintegrating agents, each mini tablet containing 2mg Repaglinide. Sustained release mini tablet (SRMT) were formulated using various polymers, each mini tablet containing 4mg Repaglinide. The prepared mini tablets were subjected to pre and post compressional parameters and the values were within the prescribed limits. The drug- excipient compatibility studies were performed using FTIR techniques. The invitro performance showed the desired biphasic behavior with 99.7% drug release within 15 mins using SSG as superdisintegrating agent in IRMT and combination of HPMC K100M and Ethyl cellulose in SRMT was found to be suitable approach to release the drug over 10 hr time period. Capsules were filled with individual mini tablets to deliver 6mg of Repaglinide designed to provide a multi particulate delivery of drug as immediate and sustained dissolution release profiles.

Keywords: Biphasic, Floating mini tablets, Superdisintegrating agents, Repaglinide.

INTRODUCTION

Pharmaceutical dosage forms

Dosage forms are the means by which drug molecules are delivered to sites of action within the body.

The need for dosage forms

1. Accurate dose
2. Protection e.g. coated tablets , sealed ampoules
3. Protection from gastric juice
4. Masking taste and odour
5. Placement of drugs within body tissues
6. Sustained release medication
7. Controlled release medication
8. Optimal drug action
9. Insertion of drugs into body cavities (rectal , vaginal)
10. Use of desired vehicle for insoluble drugs.

Classification

1. According to route of administration: oral, topical, rectal parenteral, vaginal, inhaled, ophthalmic, otic.
2. According to physical form: solid , semisolid , liquid [1]

Solid dosage forms include; powders, granules, tablets, capsules and suppositories (suppositories may be also classified as semi-solid dosage form). [2]

Controlled release dosage form

It is a dosage form that releases one or more drugs continuously in predetermined pattern for a fixed period of time, either systemically or locally to specified target organ controlled release dosage forms provides better control of plasma drug levels,

less dosage frequency, less side effect, increased efficacy and constant delivery. [3]

Classification

Oral controlled release drug delivery systems can be classified in two broad groups:

1. Single unit dosage forms (SUDFs) , such as tablets or capsules , and
2. Multiple unit dosage forms (MUDFs), such as granules, pellets or mini tablets.

Mini tablets

Mini tablets are flat or curved tablets with a 1.0-3.0 mm diameter which, for pharmaceutical use, are normally filled in hard gelatin capsules. Mini tablets can be an alternative to normally sized tablets, if there are specific preparation requirements as regards the following aspects: [4]

- Release profile/ drug absorption
- Constituents
- A comparison of pellets/ mini tablets
- Outlook

Formulation of mini-tablet-in-capsule systems

The formulation process of mini-tablet-in-capsule systems includes the following steps:

- The formulation/production of immediate release mini-tablets
- The formulation/production of sustained release mini-tablets
- Filling of mini-tablets-in-capsule. [5]

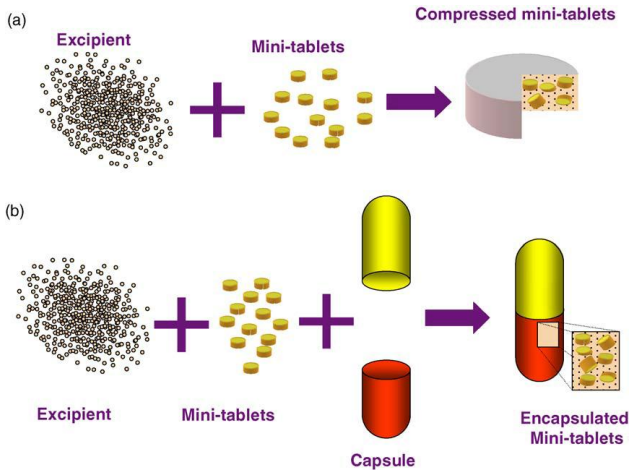

Fig 1: compressed mini tablets, encapsulated mini tablets

MATERIALS AND METHODS

Table 1: List of materials

S. No	Materials
1	Repaglinide
2	Magnesium stearate
5	Cross Povidone
6	Sodium Starch Glycolate
7	Cross Carmellose Sodium
8	Microcrystalline Cellulose
9	Hydroxyl propyl methyl cellulose K4M
10	Hydroxyl propyl methyl cellulose K15M
11	Hydroxyl propyl methyl cellulose K100M
12	Ethyl cellulose
13	Sodium bicarbonate

Table 2: Immediate release Repaglinide mini tablets IF1-IF6

Ingredients (mg)	IF1	IF2	IF3	IF4	IF5	IF6
Repaglinide	2	2	2	2	2	2
Sodium Starch Glycolate	2.5 (5 %)	5 (10 %)	-	-	-	-
Cross Povidone	-	-	2.5 (5 %)	5 (10 %)	-	-
Cros Carmellose Sodium	-	-	-	-	2.5 (5 %)	5 (10 %)
Magnesium Stearate	1	1	1	1	1	1
Avicel	44.5	42	44.5	42	44.5	42
Total weight	50	50	50	50	50	50

Table 3: Sustained release Repaglinide mini tablets SF1 – SF7

Ingredients (mg)	SF1	SF2	SF3	SF4	SF5	SF6	SF7
Drug	2	2	2	2	2	2	2
HPMC K4M	16 (20%)	24 (30%)	-	-	-	-	-
HPMC K15M	-	-	16 (20%)	24 (30%)	-	-	-
HPMC K100M	-	-	-	-	16 (20%)	24 (30%)	12 (15%)
Ethyl cellulose	-	-	-	-	-	-	12 (15%)
Magnesium Stearate (2.5 %)	2	2	2	2	2	2	2
$NaHCO_3$ (15 %)	12	12	12	12	12	12	12
MCC	37	12	37	12	37	12	2
Tablet weight	80	80	80	80	80	80	80

RESULTS

Preformulation study

UV spectrum of Repaglinide in 0.1N HCl

UV spectrum of Repaglinide in 0.1N HCl shows that the drug had a λ_{max} of 242nm.

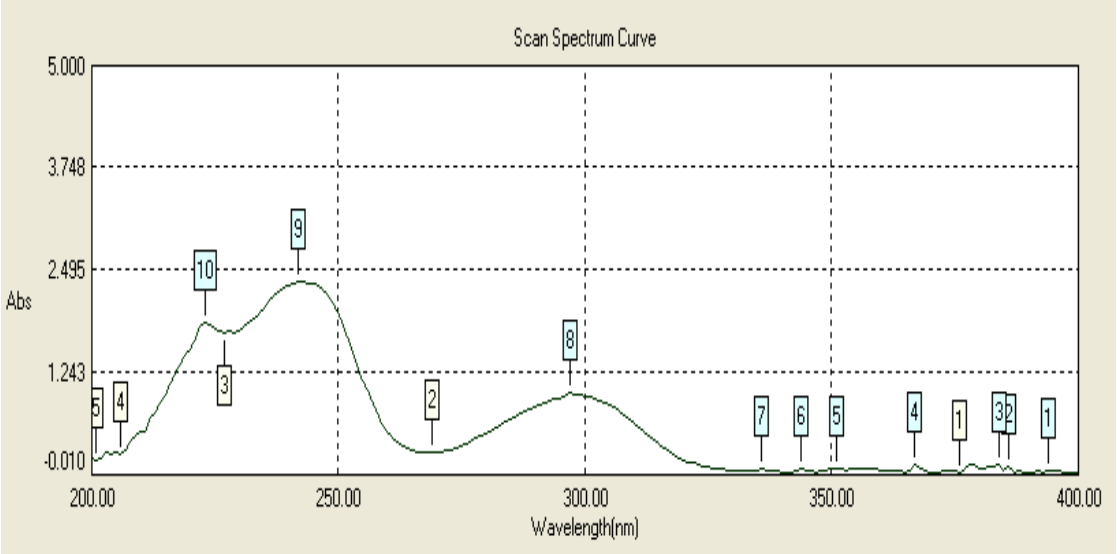

Fig 2: UV spectrum of Repaglinide

Standard plot of repaglinide in 0.1N HCl

The standard plot of Repaglinide in 0.1N HCl is shown in figure. The data of absorbance is shown in table. The correlation coefficient obtained was 0.999. [6]

Table 4: Standard plot of repaglinide in 0.1N HCl

Concentration (µg/ml)	Absorbance
0	0
0.5	0.110
1.0	0.245
1.5	0.365
2.0	0.493
2.5	0.638

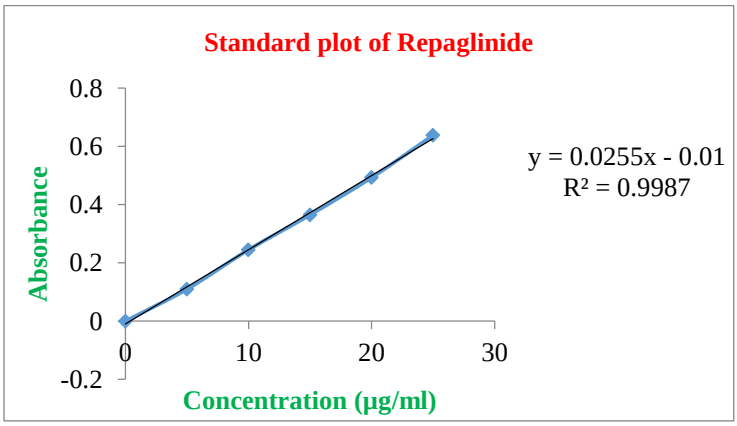

Fig 3: Standard plot of Repaglinide in 0.1N HCl

Drug-excipients interaction study

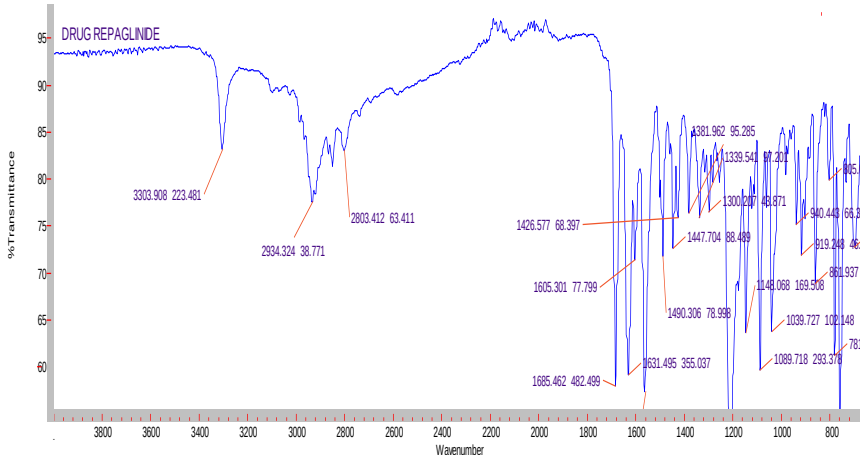

Fig 4: FTIR spectra of Repaglinide

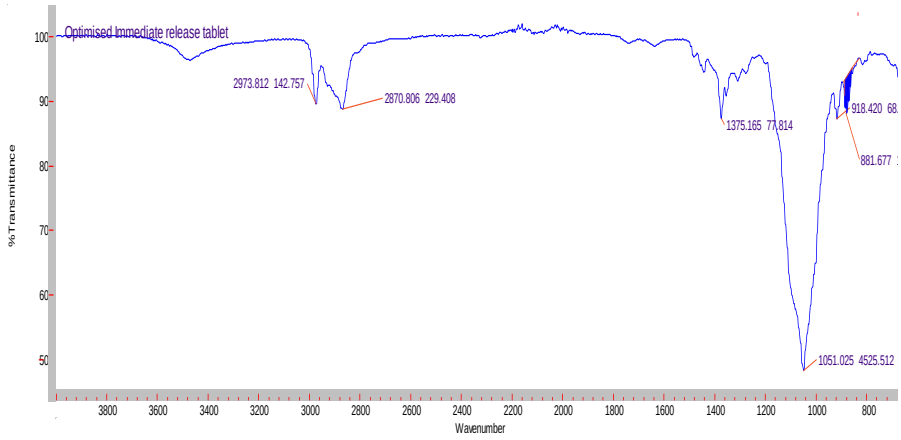

Fig 5: FTIR spectra of optimised immediate release tablet of Repaglinide

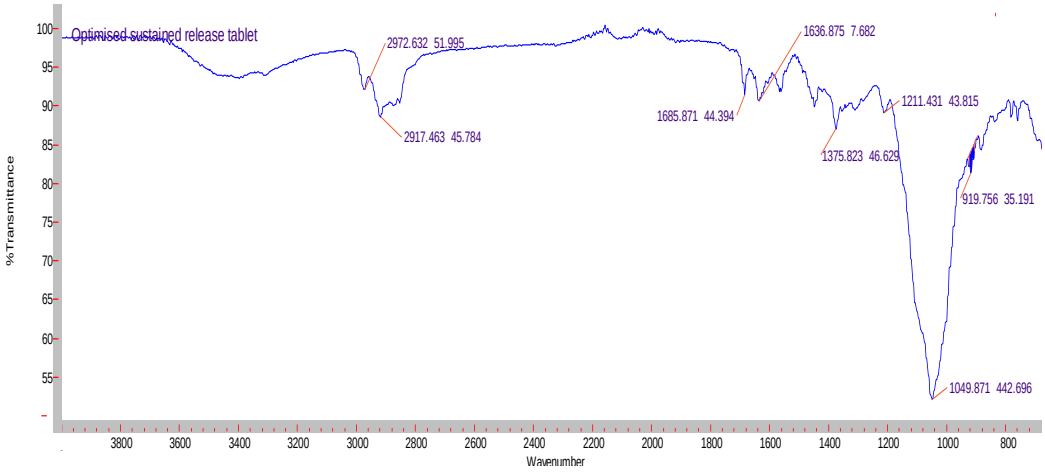

Fig 6: FTIR spectra of optimized sustained release tablet of Repaglinide

DISCUSSION

The drug Repaglinide exhibited a λ_{max} of 242nm which was same as reported in graph .The standard curve in 0.1N HCl was found to be linear with R^2 value of o.9987and slope as shown. Physical mixtures of drug and excipients were characterized by FTIR spectral analysis for any physical as well as chemical alteration of the drug characteristics. Results showed no interaction between drug and excipients. [7]

Table 5: FT-IR data interpretation

Formulations	Wave number in formulation((cm^{-1})	Characteristic wave number range(cm^{-1})	Bond nature and bond attributed
Pure drug	3303.90	3200-3400	NH stretching
SSG	1590.47	1400-1600	C=C ring stretch Benzene
HPMC K100M	2900.51	2800-3000	OH stretching (Bonded)
Ethyl Cellulose	1739.74	1600-1800	C=O saturated acyclic stretching of aldehyde
Optimized IRMT	2973.81	2800-3000	C-H aliphatic stretching of aldehyde
Optimized SRMT	2917.48	2800-3000	C-H aromatic stretching

Six formulations of immediate release mini tablet were prepared using various super disintegrating agents as described in methodology. 11 formulations of floating sustained release mini tablet were prepared using various polymers alone and in combination as described in methodology. [8]

Pre -compression parameters

The drug and excipients used in the immediate release as well as sustained release formulation evaluated for bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose as per the procedure described under methodology. [9]

Post compression parameters

Thickness of tablets

Thickness of mini tablets was measured by vernier callipers using the procedure described in methodology. The diameter of all the formulations were found within the acceptable range. [10]

Hardness of tablets

The hardness of all formulations were checked by using Monsanto Hardness tester by the method described in methodology. The average hardness of immediate release and sustained formulations were in the range of.

Friability of tablets

The friability of all the formulations was checked using Labindia FT 1020 tablet Friability tester according to the procedure in methodology. The average friability for all the formulations were in the range of.

Weight variation test

Uniformity of weight test for all the formulations were carried out using the procedure described in the methodology. Results of uniformity of weight are shown in the table no. All the formulations were came under the acceptable limit and results are shown.

Disintegration time test

This test is done for the immediate release mini tablet the purpose of which is quick release of drug. Therefore this mini tablet should disintegrate immediately for drug to be readily available for dissolution and absorption. Disintegration time mainly depends upon the concentration of disintegrant. The disintegration time of IRMT was found to be 6mins. The disintegration times are shown.

Buoyancy determination

Determination of Buoyancy Lag Time (BLT) was only performed to check the floating

behaviour of floating sustained release mini tablet. The buoyancy of floating sustained release mini tablet was studied at 37 ± 0.5^{o}C in 200 ml of 0.1N HCl. The buoyancy lag time (BLT) was measured by using stop watch and total floating time was observed visually**.** Floating lag time was observed less than 90sec for all batches. Total floating time was observed more than 24hrs. The results are shown. To study the release kinetics, *in vitro* dissolution data obtained from optimized formulations were applied to various kinetic models viz. Zero order, first order, Higuchi release and Korsemeyer-peppas equation.

To confirm the exact mechanism of drug release from these tablets the data were fitted according to the Korsmeyer-Peppas equation. When n takes the value of 0.5, it indicates diffusion controlled drug release and for the value 1.0 it indicates swelling controlled drug release. Values of n between 0.5 and 1.0 can be regarded as an indicator for both phenomena (Anomalous transport).The value of n in case of optimized formulation was between 0.5 and 1.0 suggested that the release of Repaglinide sustained release mini tablet followed the anomalous transport mechanism. This means diffusion as well as swelling controlled had an essential role in drug release. [11]

Swelling study

Swelling study was performed on all batches of floating sustained release for 6 hrs. From the results it was concluded that swelling increases as the time passes because the polymer gradually absorb water due to hydrophilicity of the polymer. The viscosity of the polymer had major influence on swelling process, matrix integrity, as well as floating capability, hence from the results it can be studied that linear relationship exists between swelling process and viscosity of polymer.

In-vitro drug release studies

In-vitro drug release studies were performed as per the procedure described in methodology. The percentage cumulative drug release was plotted against time to obtain drug release profiles. The results are shown in table and figure(14-19 for IRMT, 23,24 for SRMT). The percentage drug released in the first 30 min was similar in the all formulations. However, in IRMT IF2, 99.7 % of the Repaglinide was released within the first 15 min, and the content of disintegrant in the tablet significantly inclined AFC release.

In-vitro release tests were carried out for SRMT. Repaglinide release profiles from SRMT contain with different polymer ratio. In the optimized formulation SRMT SF7 90% of the Repaglinide would be released within 8 hrs and 96.23 % within 10 hrs.

In-vitro release tests was also carried out for the capsule containing optimised IRMT and SRMT. In the first phase the loading dose(immediate release) was released in less than 15 mins, because of the prompt disintegration of the fast releasing mini tablet and enhanced rate of dissolution of Repaglinide from the system. The maintenance dose was carried further by SRMT.

Table 6: Evaluation of thickness, hardness, friability and weight variation if immediate releas tablets

Formulation	Thickness[A] (mm)	Hardness[B] (kg/cm^2)	Friability (%)	Weight variation (mg), n=3
IF1	2.26 ± 0.025	3.0 ± 0.070	0.38	50 ± 0.46
IF2	2.21 ± 0.016	3.0 ± 0.110	0.37	50 ± 0.24
IF3	2.20 ± 0.0264	3.0 ± 0.230	0.39	49 ± 1.13
IF4	2.25 ± 0.0316	3.2 ± 0.141	0.43	49 ± 1.21
IF5	2.24 ± 0.010	3.1 ± 0.223	0.47	50 ± 0.76
IF6	2.30 ± 0.030	3.0 ± 0.234	0.48	50 ± 0.93

Table 7: Evaluation of sustained release mini tablets

Formulations	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Weight variation (mg)
SF1	2.51 ± 0.0381	3.1 ± 0.10	0.45	80 ± o.35
SF2	2.59 ± 0.025	3.4 ± 0.173	0.51	80 ± 0.46
SF3	2.47 ± 0.0361	3.5 ± 0.308	0.38	79 ± 0.29
SF4	2.52 ± 0.0308	3.3 ± 0.316	0.42	80 ± 0.41
SF5	2.57 ± 0.030	3.0 ± 0.141	0.35	78 ± 1.21
SF6	2.42 ± 0.055	3.4 ± 0.308	0.49	79 ± 0.78
SF7	2.41 ± 0.0254	3.1 ± 0.173	0.33	80 ± 0.11

Release kinetics

Various mathematical models were selected to evaluate the kinetics and mechanism of drug release from immediate and sustained release mini tablet formulation. Best model was selected for release data which showed high correlation coefficient (r) value. The mechanism of release for the optimized mini tablet formulation was based on regression coefficient (r2) value It can be concluded that the drug release follow first order model.

Accelarated stability studies

The optimized formulation was found to be stable after exposure to accelerated temperature and humidity conditions for a period of 3 months. No significant changes were seen in physical evaluation parameters as shown.

Pre compression parameters

Table 8: Invitro dissolution study

Time (hrs)	SF1	SF2	SF3	SF4	SF5	SF6	SF7
0	0	0	0	0	0	0	0
0.5	44.5	37.6	42.6	32.3	28.89	32.45	20.19
1	69.7	49.8	59.2	68.5	44.6	43.99	38.22
2	88	64.9	63.9	79.2	69.2	53.36	54.56
3	97.3	89.3	72.8	90.86	85.81	64.75	61.29
4	102.16	99.9	95.19	95.192	98.79	72.83	70.67
6						83.65	86.53
8						97.3	90.14
10							96.23

Table 9: Drug release kinetics

Cumulative (%) Release Q	Time T	Root T	Log % Release	Log T	Log % Remain	Release Rate (Cumulative % Release / T)
0	0	0			2.000	
20.19	0.5	0.707	1.305	-0.301	1.902	40.380
38.22	1	1.000	1.582	0.000	1.791	38.220
54.56	2	1.414	1.737	0.301	1.657	27.280
61.29	3	1.732	1.787	0.477	1.588	20.430
70.67	4	2.000	1.849	0.602	1.467	17.668
86.53	6	2.449	1.937	0.778	1.129	14.422
90.14	8	2.828	1.955	0.903	0.994	11.268
96.23	10	3.162	1.983	1.000	0.576	9.623

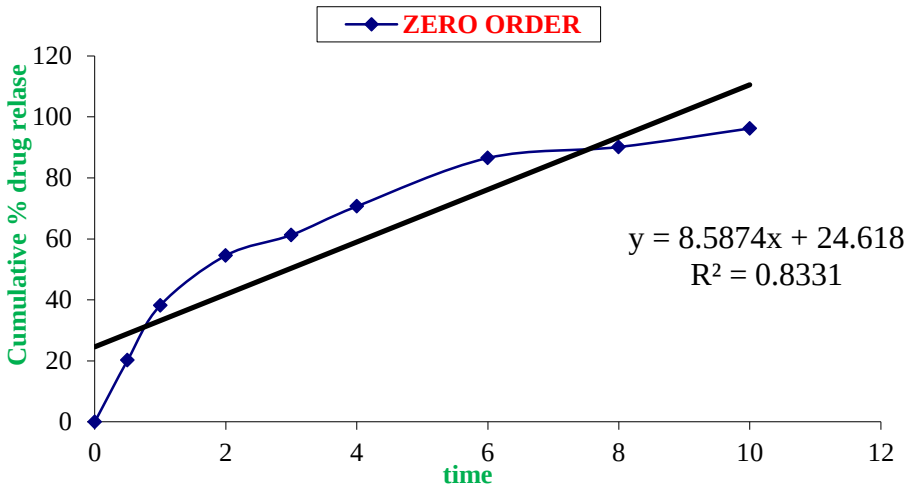

Figure 7: Zero order release of optimized sustained release formulation SF7

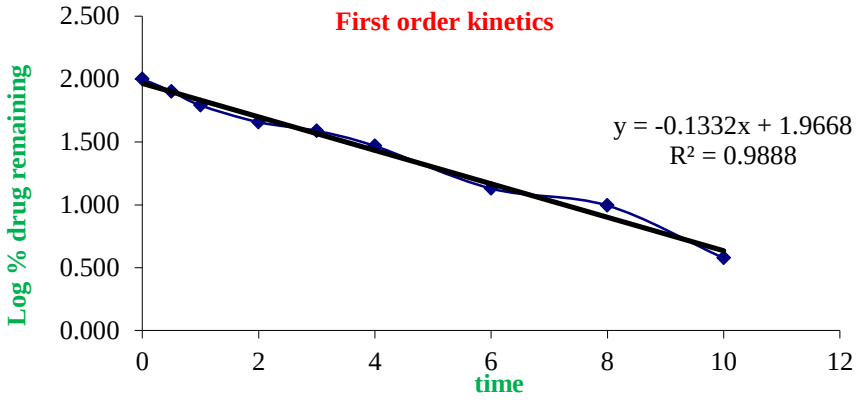

Fig 8: First order release of optimized sustained release formulation SF7

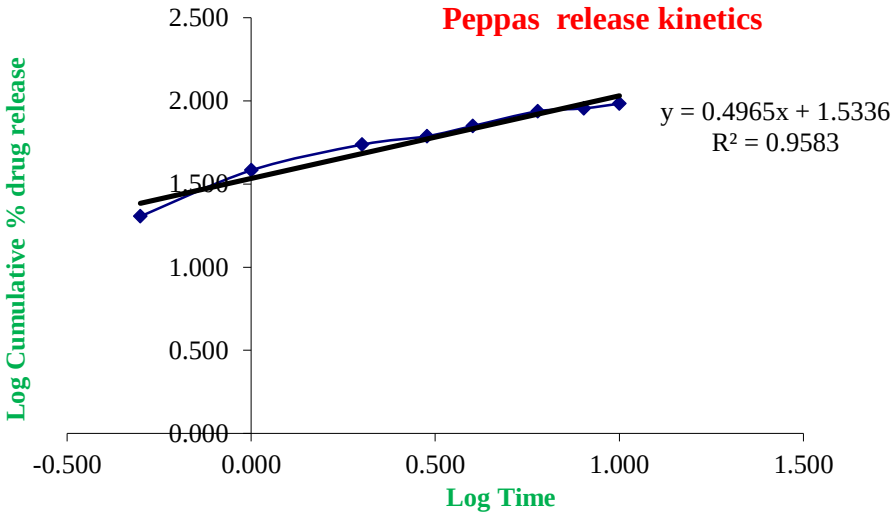

Fig 9: Peppas for release of optimised sustained release formulation SF7

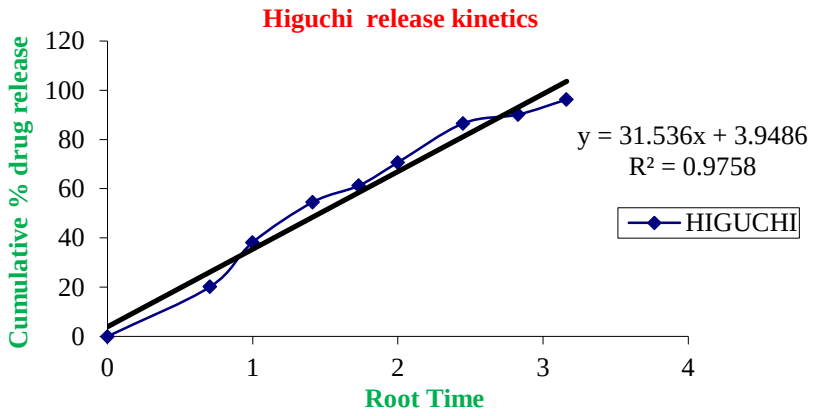

Fig 10: Higuchi for release of optimized sustained release formulation SF7

Table 10: Accelarated stability studies of optimized formulation

Stability period	% drug content	%in vitro release
Initial	98 ± 0.20	96.23
30 days	97.97 ± 0.14	96.10
60 days	97.86 ± 0.11	95.95
90 days	97.66 ± 0.10	95.87

CONCLUSION

In the present study, an attempt was made to develop a biphasic mini tablets in a capsule system containing immediate and floating sustained release mini tablet. Because of their physical characteristics, mini-tablets tend to keep their integrity after compression, making more difficult the fracturing process of these subunits.

IF2 was optimised in IRMT containing SSG as a super disintegrating agent and SF7 was optimised in SRMT containing HPMC K100M and Ethyl cellulose along with other common tablet excipients to control as well as extend the drug release over a period of 10 hrs. The optimised mini tablets placed in a capsule showed satisfactory results in several in vitro tests. Number of mini tablets can be filled depending upon the size of the capsule shell and the diameter or weight of mini-tablets.

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