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Gastro-retentive drug delivery system of hypertension drug: Formulation and evaluation study

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Abstract

Introduction: Hypertension, a major global health concern, necessitates effective management through sustained drug delivery systems. Gastro-retentive drug delivery systems (GRDDS) offer a strategic advantage by prolonging the residence time of drugs in the stomach, thus enhancing therapeutic efficacy and patient adherence. This study aims to develop and evaluate a GRDDS for antihypertensive drugs to achieve extended gastric retention and controlled release.

Methods: A GRDDS was formulated using a combination of hydrophilic and hydrophobic polymers to ensure buoyancy and extended gastric retention. The formulation process involved selecting optimal polymer concentrations and incorporating release-modulating agents. In vitro evaluations included buoyancy studies, swelling behavior analysis, and drug release kinetics under simulated gastric conditions. Additionally, in vivo studies were conducted to assess the system's gastric retention and pharmacokinetic profile in an animal model.

Conclusion: The developed GRDDS demonstrated effective gastric retention and a controlled release profile for the antihypertensive drug. In vitro results confirmed the system's ability to maintain buoyancy and provide sustained drug release. In vivo studies supported these findings, showing improved drug bioavailability and stable plasma levels. This GRDDS represents a promising advancement in hypertension management, potentially enhancing therapeutic outcomes and patient compliance. Further research and clinical trials are recommended to validate these preclinical results and optimize the system for broader application.

Keywords: Gastro-retentive Drug Delivery System (GRDDS); Antihypertensive Drug; Controlled Release; Formulation

1. Introduction

1.1. Gastro-retentive Drug Delivery System

Oral administration is the most convenient and preferred means of any drug delivery to the systematic circulation [1]. Oral controlled release drug delivery have recently been of increasing interest in pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in formulation. Drugs that are easily absorbed from gastrointestinal tract (Gin and have short half-lives are eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve suitable therapeutic activity. To avoid this limitation, the development of oral sustained-controlled release formulations is an attempt to release the drug slowly into the gastrointestinal tract (GIT) and maintain an effective drug concentration in the systemic circulation for a long time. After oral administration, such a drug delivery would be retained in the stomach and release the drug in a controlled manner, so that the drug could be supplied continuously to its absorption sites in the gastrointestinal tract (GIT) [2]. These drug delivery systems suffer from mainly two adversities: the short gastric retention time (GRT) and

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unpredictable short gastric emptying time (GEn, which can result in incomplete drug release from the dosage form in the absorption zone (stomach or upper part of small intestine) leading to diminished efficacy of administered dose [3, 4]. To formulate a site-specific orally administered controlled release dosage form, it is desirable to achieve a prolong gastric residence time by the drug delivery. Prolonged gastric retention improves bioavailability, increases the duration of drug release, reduces drug waste, and improves the drug solubility that are less soluble in a high pH environment. Also prolonged gastric retention time (GRT) in the stomach could be advantageous for local action in the upper part of the small intestine e.g. treatment of peptic ulcer, etc. [5]. Gastro retentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (Gin for local or systemic effects. Gastro retentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time (GRT) of drugs [6]. Over the last few decades, several gastro retentive drug delivery approaches being designed and developed, including: high density (sinking) systems that is retained in the bottom of the stomach , low density (floating) systems that causes buoyancy in gastric fluid mucoadhesive systems that causes bio adhesion to stomach mucosa , unfoldable, extendible systems which limits emptying of the dosage forms through the pyloric sphincter of stomach ,superporous hydrogel systems , magnetic systems etc. [7]. The current review deals with various gastro retentive approaches that have recently become leading methodologies in the field of site-specific orally administered controlled release drug delivery systems. The oral route is considered as the most promising route of drug delivery. Effective oral drug delivery may depend upon the factors such as gastric emptying process, gastrointestinal transit time of dosage form, drug release from the dosage form and site of absorption of drugs [8, 9]. Most of the oral dosage forms possess several physiological limitations such as variable gastrointestinal transit, because of variable gastric emptying leading to non-uniform absorption profiles, incomplete drug release and shorter residence time of the dosage form in the stomach [10]. This leads to incomplete absorption of drugs having absorption window especially in the upper part of the small intestine, as once the drug passes down the absorption site, the remaining quantity goes unabsorbed [11, 12]. The gastric emptying of dosage forms in humans is affected by several factors because of which wide inter and intra-subject variations are observed [13, 14, 15]. Since many drugs are well absorbed in the upper part of the gastrointestinal tract, such high variability may lead to non-uniform absorption and makes the bioavailability unpredictable. Hence, a beneficial delivery system would be one which possesses the ability to control and prolong the gastric emptying time and can deliver drugs in higher concentrations to the absorption site (i.e. upper part of the small intestine) [16, 17]. The identification of new diseases and the resistance shown towards the existing drugs called for the introduction of new therapeutic molecules [18]. In response, a large number of chemical entities have been introduced, of which some have absorption all over the gastrointestinal tract (GIT), some have absorption windows (i.e. absorption sites), especially the upper part of the small intestine and some drugs have poor solubility in intestinal media [19, 20]. The drugs belonging to the second and third categories, and the drugs which are required for local action in the stomach, require a specialized delivery system. All the above requirements can be met and effective delivery of the drugs to the absorption window, for local action and for the treatment of gastric disorders such as gastro-esophageal reflux, can be achieved by floating drug delivery systems (FDDS) [21, 22].

1.2. Drugs reported to be used in the formulation of floating dosage forms are:

Floating microspheres (aspirin, griseofulvin, p-nitroaniline, ibuprofen, terfinadine and tranilast), [23] floating granules (enalapril, indomethacin and prednisolone), [24] films (cinnarizine), floating capsules (chlordiazepoxide hydrogen chloride, perindopril , furosemide, misoprostol, L-Dopa, [25] benserazide, ursodeoxycholic acid and pepstatin) and floating tablets and pills (ramipril, , ampicillin, amoxycillin trihydrate, atenolol, diltiazem, fluorouracil, isosorbide mononitrate, para aminobenzoic acid, piretamide, theophylline and verapimil hydrochloride, etc.) [26, 27]. Excipients used most commonly in these systems include HPMC, polyacrylate polymers, polyvinyl acetate, Carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates [28, 29, 30]. Fig. 1

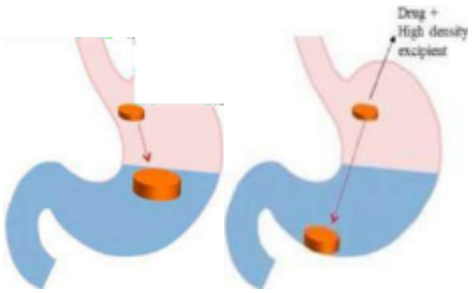

Figure 1 The floating drug delivery in stomach

2. Material and methods

2.1. Stability studies

In designing a solid dosage form it is necessary to know the inherent stability of the drug substance, to have an idea of what excipients to use, as well as how best to put them together with the drug and to know that no toxic substance are formed. Limits of acceptability and therefore compromises must be reasonably defined. Because the measurements of these aspects of stability as well as determination of shelf life or expiration date for the final dosage form require long term stability studies for confirmation, they can be expensive and time consuming. Consequently it is necessary to define those study designs and conditions that show the greatest probability of success. The objective therefore of a stability study is to identify and help avoid or control situations where the stability of the active ingredient may be compromised. For a drug substance to be developed into a tablet dosage form, this objective may be achieved by investigating the stability of the drug under the following three categories,

- solid state stability of drug alone,
- compatibility studies in presence of excipients,
- solution phase stability.

Rationale for stability studies:

There may be chemical degradation of active drug leading to a substantial lowering of the quantity of therapeutic agent in the dosage form.

Although chemical degradation of the active drug may not be expensive, a toxic product may be formed in the decomposition process.

Instability of drug product can lead to substantial lowering in the therapeutic efficiency of the dosage form.

2.2. Types of stability studies:

Basically there are two types of stability studies

- Short-term stability study.
- Long-term stability study

A typical short-term stability study is an accelerated stability testing study under stressed storage conditions. The purpose of it is not only to determine the rate of chemical and physical reactions but also predict a tentative expiration-dating period under ambient marketing conditions.

The accelerated stability study is useful in the following ways:

- The results provide estimate of the kinetic parameters for the rate of reactions.
- The results can be used to characterize the relationship between degradation and storage condition.
- The results supply critical information in the design and analysis of long-term stability studies under ambient conditions at the planning stage.
- Long term stability study, which includes both preapproval, and post approval stability studies, is usually conducted under ambient condition.
- A pre-approval stability study is also known as NDA stability study, the purpose of it is to determine (estimate) a drug expiration dating applicable to all future batches.
- A post approval stability study is usually referred to as a marketing stability study, the purpose of it is to make sure that the drug product currently on market can meet the USP/ NF specifications up to the end of expiration dating period.

Table 1 ICH guidelines for stability study

Study Type	Storage Condition	Temperature	Relative Humidity (%)	Minimum Time
Long Term	25°C ± 2°C	60% ± 5% RH	12 Months	
Intermediate	30°C ± 2°C	65% ± 5% RH	6 Months	
Accelerated	40°C ± 2°C	75% ± 5% RH	6 Months	

Part I:

2.2.1. Achieving of 60% RH:

26.66 gm of sodium hydroxide was weighed and dissolved in 100 ml of distilled water to get 26.66% sodium hydroxide solution. The solution was placed in the desiccator over which a wire mesh was placed, over which the dosage form was placed and the desiccator was sealed. The desiccator was placed in the oven maintained at 25°C to create the Relative Humidity OF 60%.

2.2.2. Achieving of 75% RH

Saturated solution of sodium chloride was prepared and placed in the desiccators over which a wire mesh was placed, over which the dosage form was placed and the desiccator was sealed. The desiccator was kept in oven maintained at 40°C to create the relative humidity of 75%.

Part II

The sealed formulation were placed in ambered colored bottles, tightly plugged with cotton and capped. They were then stored at 25°C /60% RH and 40°C / 75% RH for two months and evaluated for their physical appearance and drug content. Table 1

Table 2 Concentration (µg/mL) Absorbance in HCl Absorbance in Phosphate Buffer (pH 7.4)

S.No	Concentration (µg/mL)	Absorbance in HCl	Absorbance in Phosphate Buffer (pH 7.4)
1	0	0	0
2	2	0.038	0.153
3	4	0.0646	0.320
4	6	0.116	0.480
5	8	0.165	0.614
6	10	0.191	0.770
7	12	0.238	0.936

Equations: For HCl: Y=0.0198Y = 0.0198Y=0.0198 with R2=0.9976R^2 = 0.9976R2=0.9976

For Phosphate Buffer (pH 7.4): Y=0.0774Y = 0.0774Y=0.0774 with R2=0.9994R^2 = 0.9994R2=0.9994

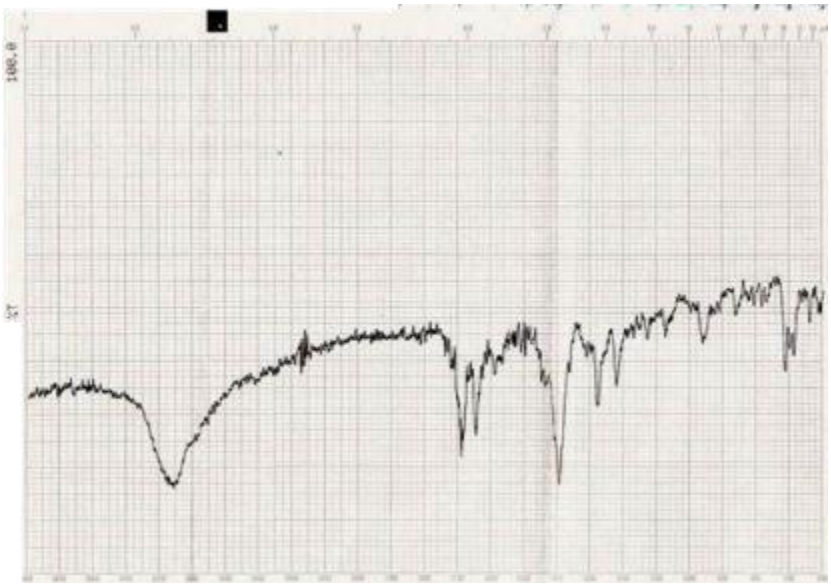

Figure 2 I.R. spectrum of candesartan cilexetil

Table 3 Composition data for Candesartan Cilexetil Floating Tablets

Ingredients	FT1	FT2	FT3	FT4	FT5	FT6	FT7	FT8	FT9	FT10
Candesartan Cilexetil	200	200	200	200	200	200	200	200	200	200
HPMC K15M	180	-	-	90	90	-	90	-	-	60
HPMC K50M	-	180	-	90	-	90	45	90	-	60
Ethyl Cellulose	-	-	180	-	90	90	-	90	-	60
Sodium Bicarbonate	80	80	80	80	80	80	80	80	80	80
Citric Acid (Anhydrous)	20	20	20	20	20	20	20	20	20	20
Stearate	-	-	-	-	-	-	-	-	-	-

Table 4 The micrometric properties data for the powder blend

Powder Blend	Angle of Repose (°)	Loose Bulk Density (g/ml)	Tapped Bulk Density (g/ml)	Compressibility Index (%)	Hausner Ratio
FT1	24°.50'	0.131	0.156	16.02	1.19
FT2	-	0.112	0.128	15.62	1.14
FT3	25°.35'	0.092	0.108	14.81	1.20
FT4	28°.60'	0.110	0.132	16.66	1.20
FT5	-	0.123	0.145	15.17	1.17
FT6	-	0.113	0.132	14.39	1.16
FT7	-	0.133	0.152	12.50	1.14
FT8	-	0.135	0.154	13.47	1.14
FT9	26°.68'	0.140	0.160	12.35	1.42
FT10	28°.82'	0.110	0.130	15.38	1.18

Table 5 Effect of different polymers on drug release by paddle method data

Time (hrs.)	FT1	FT2	FT3	FT4	FT5	FT6	FT7	FT8	FT9	FT10
0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
1	2.48	4.32	1.54	3.41	1.94	2.24	2.48	3.86	1.24	2.36
2	4.36	6.86	2.26	5.80	3.78	3.94	4.78	5.24	2.58	5.48
3	6.41	6.46	4.80	7.68	5.24	6.52	6.58	7.94	5.91	8.32
4	9.43	12.99	6.48	10.20	8.40	8.40	8.60	10.32	8.24	10.64
5	13.88	18.46	9.42	14.86	11.82	11.82	12.32	14.30	10.28	13.40
6	17.34	20.16	10.37	16.30	14.86	14.86	16.60	17.49	12.24	16.86
7	20.15	25.36	14.78	22.40	18.82	18.82	20.28	22.26	16.22	20.34
8	25.28	30.42	19.38	28.84	22.42	22.42	26.28	28.68	20.98	24.30
9	29.38	37.22	22.60	32.52	24.42	24.32	30.48	32.56	22.30	27.40
10	32.46	39.46	25.80	35.92	28.51	28.51	32.18	35.30	26.28	30.28
24	60.58	49.46	30.82	45.30	35.42	35.42	44.26	47.28	32.24	38.81
FLT (sec.)	175	102	NO	95	136	NO	100	78	190	45
TFT (hrs)	8	8	NO	12	12	NO	>12	6	8	>12

FLT= Floating lag time

Table 6 Effect of different polymers on drug release by paddle method Cumulative% Drug release in phosphate buffer pH 7.4

Time (hrs)	**FT1**	**FT2**	**FT3**	**FT4**	**FT5**	**FT6**	**FT7**	**FT8**	**FT9**	**FT10**
0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
1	20.36	21.52	10.42	24.62	17.34	19.38	28.64	21.51	15.12	28.76
2	31.43	33.74	15.32	36.90	25.12	27.34	30.20	33.66	20.40	38.62
3	44.42	45.86	20.32	48.26	39.82	41.36	51.60	45.81	30.41	46.58
4	52.85	53.65	31.42	56.44	48.51	50.65	58.62	53.64	41.92	53.65
5	59.64	59.44	31.12	62.50	57.60	60.25	64.54	59.40	50.64	60.85
6	69.54	64.44	48.40	69.52	65.41	67.42	71.42	64.44	58.54	67.64
7	74.62	74.52	50.62	77.44	70.65	79.54	74.52	66.42	79.56	79.54
8	80.84	82.10	59.66	82.44	78.65	79.64	84.26	82.02	72.64	80.12
9	85.10	85.24	68.44	88.44	82.15	84.62	90.20	85.23	79.44	87.67
10	92.52	92.46	72.15	93.12	90.21	92.41	95.65	93.60	88.35	94.22

TFT= Total floating time

Table 7 Effect of hardness on Buoyancy Lag Time data

Hardness	Buoyancy Lag Time (sec)
4	52
5	61
6	
7	94
8	190

Table 8 Kinetic values obtained from in vitro released data of formulation FT07 data

Kinetic Model	Slope	R^2
Zero-order plot	8.3466	0.9366
First-order plot	-0.0041	0.9364
Higuchi plot	29.935	0.9974
Korsmeyer-Peppas	0.7212	0.9680
Hixon-Crowell	0.0298	0.9283

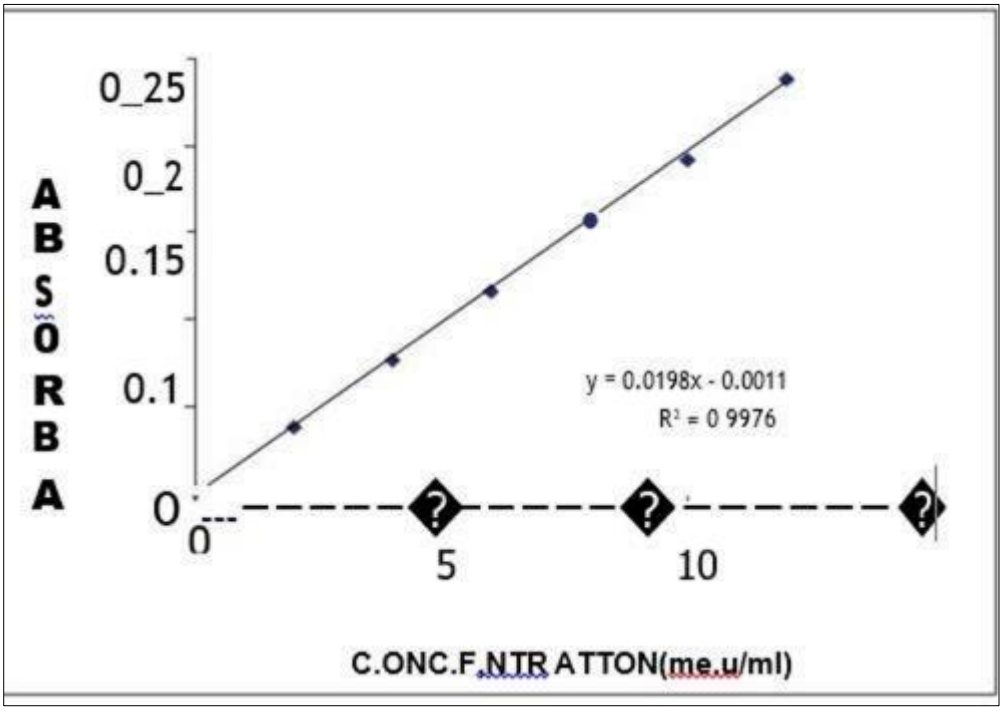

Figure 3 Standard calibration curve of candesartan Cilexetil in 0.ln HCL

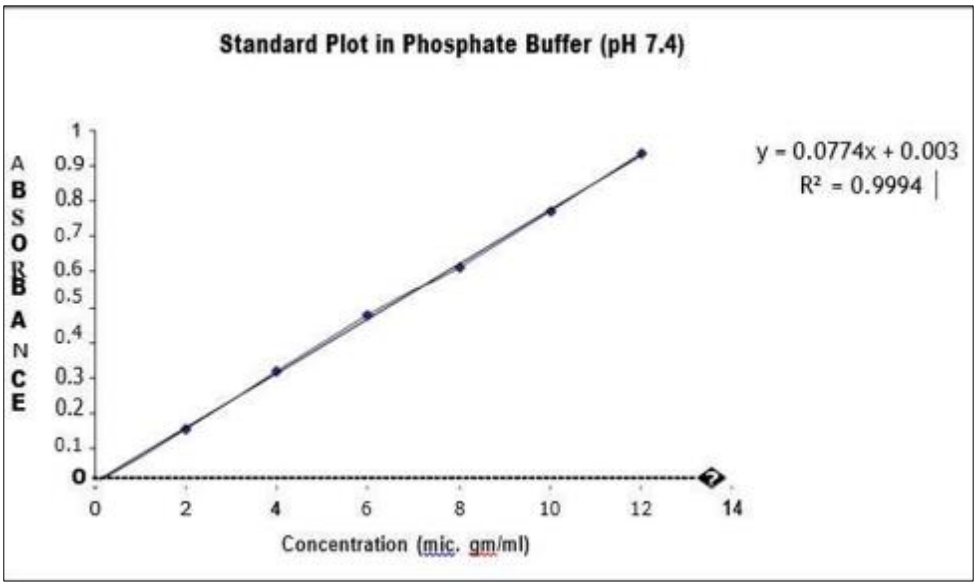

Figure 4 Standard plot in Phosphate buffer (pH 7.4)

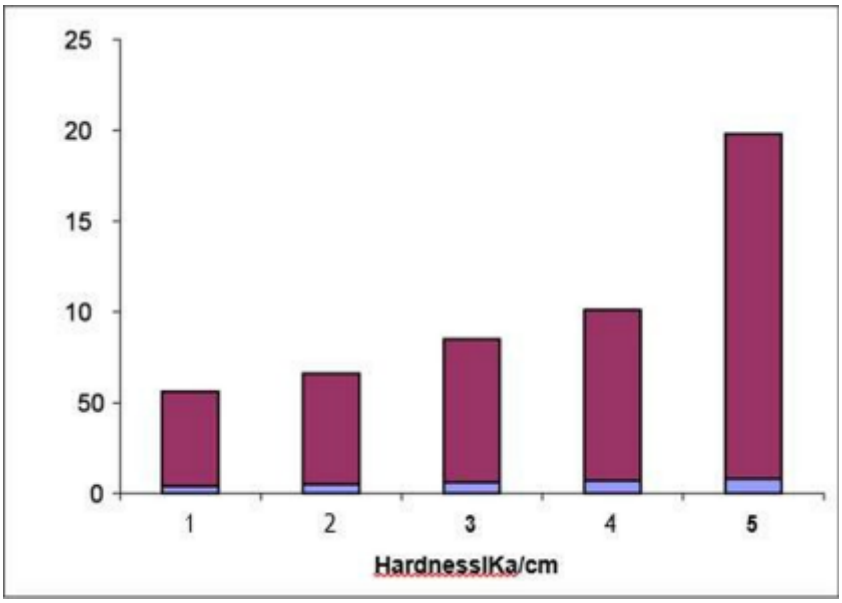

Figure 5 Plot of hardness v/s buoyancy lag time

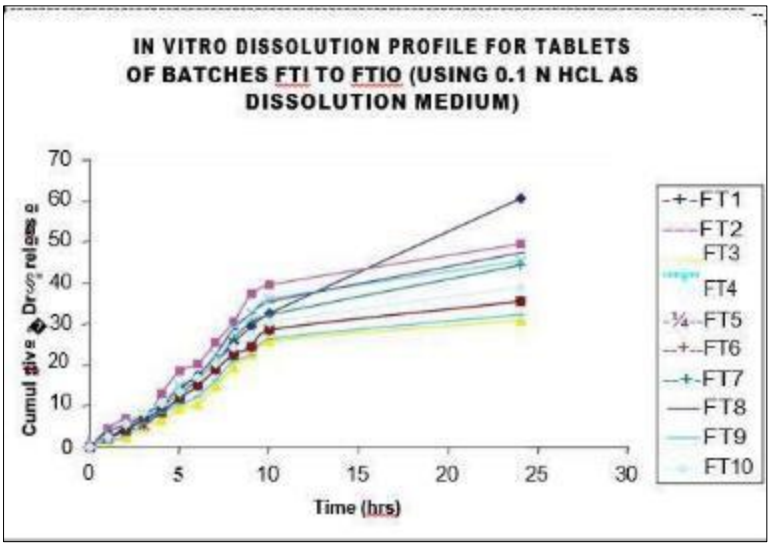

Figure 5 (a) In-vitro dissolution profile for tablets of batches FTI to FT10

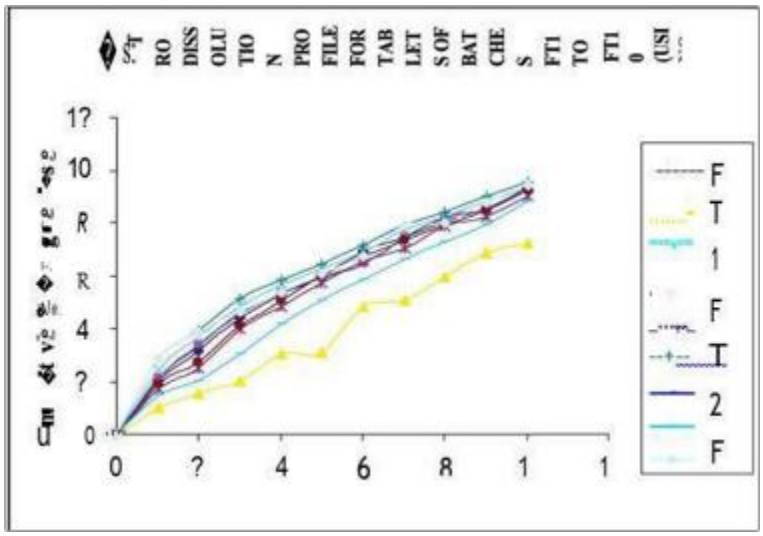

Figure 5 (b) In-vitro dissolution profile for tablets of batches FTI to FT10

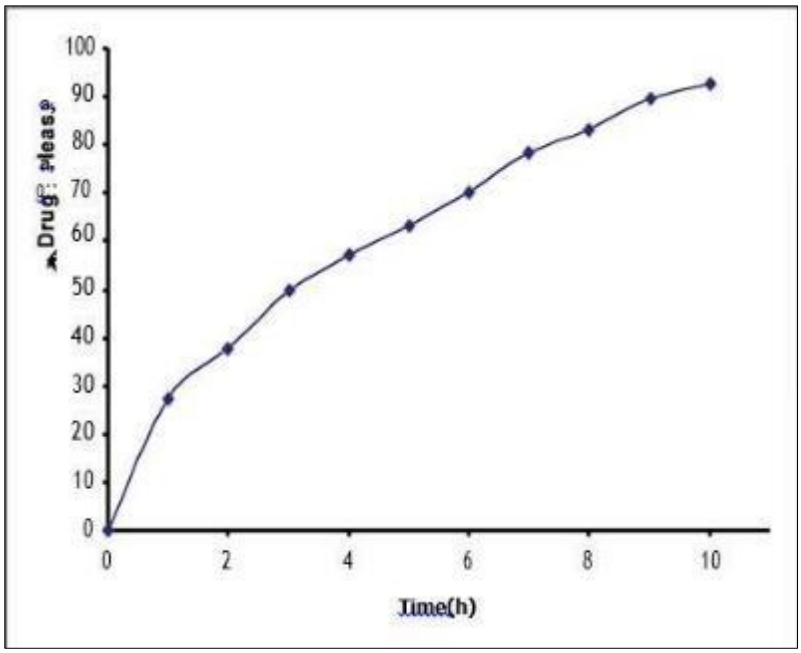

Figure 6 In vitro cumulative % drug released v/s time for formulation (ft7) of candesartan cilexetil

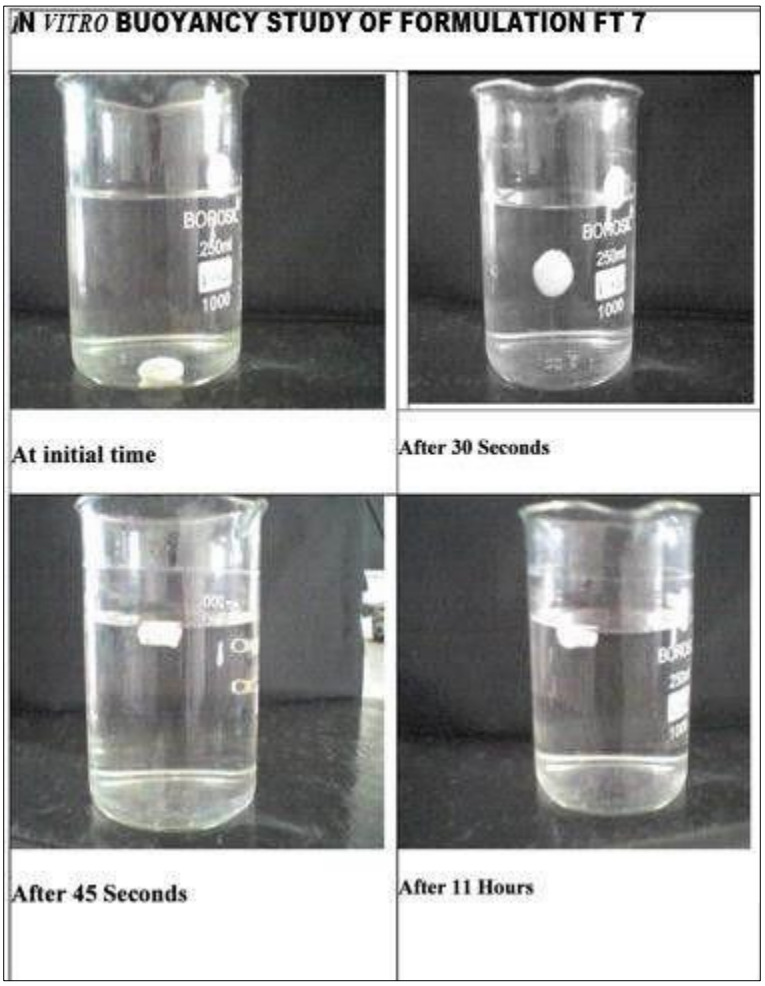

Figure 7 In vitro buoyancy study of formulation ft 8

3. Conclusion

From the compatibility studies, it was concluded that HPMC K15M, HPMC K50M, and Ethyl cellulose were compatible with Candesartan Cilexetil and thus suitable for the formulation of Candesartan Cilexetil floating tablets.

In vitro buoyancy studies were performed for all the formulations, FT 1 to FT 10 by using 0.1 N HCl solution at 37°C. All the formulations were floated except FT 3 and FT 6. The formulation FT 7 containing 90 mg of HPMC K15M, 45 mg of HPMC K50M and 45 mg of Ethyl cellulose showed more floating time (12 hours) than other formulations. In vitro dissolution studies were also performed for all formulations. The formulation FT 7 showed the controlled release for 24 hours. Thus FT 7 was identified as ideal batch based on its results.

Finally, it was concluded that HPMC K15M, HPMC K50 M and Ethyl cellulose can be successfully used in the formulation of Candesartan Cilexetil sustained release gastro retentive floating drug delivery system.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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