JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

FORMULATION AND DEVELOPMENT OF METOPROLOL SUCCINATE TABLETS IN TERMS OF FLOATING DRUG DELIVERY SYSTEM

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Abstract: The main goal of this study is to formulate and develop Metoprolol Succinate Floating tablet. To optimize Metoprolol Succinate floating tablet and carry out stability studies as per ICH guidelines. Metoprolol Succinate is classified as a BCS Class I medication, commonly prescribed for managing conditions like hypertension, angina pectoris, and heart attacks. It has a relatively short half-life, ranging from 3 to 7 hours, and its absorption can vary because of its poor solubility. Floating tablets of Metoprolol Succinate were formulated using hydrophilic polymers such as Hydroxypropyl Methylcellulose (HPMC), Carbopol, and swelling agents like calcium carbonate to create a buoyant matrix. Various formulations were developed by altering polymer content. Tablets were evaluated for parameters including hardness, thickness, weight variation, friability, drug content, floating lag time, total floating duration, swelling index, and in vitro drug release profile. The FTIR data indicates that there are no interactions of excipients with the drug. Among the formulations tested, formulation F5 exhibited the most beneficial qualities. It demonstrated a consistent drug release of 92.63% and maintained buoyancy for up to 16 hours. All key evaluation parameters such as floating lag time, swelling index, and in vitro drug release were optimized in F5 compared to other formulations. The stability study indicates that there are no significant differences in the physical parameters. The results indicate that a sustained-release floating drug delivery system for Metoprolol Succinate was successfully developed. The optimized formulation (F5) significantly improves gastric retention and drug release, making it a promising candidate for enhanced antihypertensive therapy.

Keywords: Metoprolol Succinate, Floating Drug Delivery System (FDDS), Hydrophilic Polymers, Sustained Release, In Vitro Drug Release

INTRODUCTION:

A Floating Drug Delivery System (FDDS) is a novel oral drug delivery system that is intended to increase the residence time of a drug in the stomach and increase its bioavailability. FDDS is especially useful for drugs that are absorbed mainly from the stomach or the top portion of the small intestine. In contrast to traditional oral dosage forms that move rapidly through the gastrointestinal tract, FDDS are designed to float on gastric fluids for a long time, releasing the drug gradually over time.

The buoyancy of FDDS is obtained by adding low-density ingredients or gas-forming agents to enable the dosage form to float on stomach content. They include two major forms: non-effervescent and effervescent systems. The non-effervescent systems make use of gel-forming agents, whereas the effervescent systems utilize gas-forming agents such as sodium bicarbonate, which reacts with gastric acid to form carbon dioxide.

FDDS is advantageous in improving patient compliance, decreasing dosing frequency, and increasing the therapeutic potency of drugs that have narrow windows of absorption. FDDS can be applied usefully for gastrointestinal infections, acid-related disorders, and for sustaining drug release therapy. FDDS is not adaptable for drugs that are poorly soluble in stomach fluids or acidic environments and are unstable in acidic conditions.

Metoprolol succinate is a long-acting beta-blocker widely employed in the treatment of cardiovascular diseases like hypertension, angina pectoris, and heart failure. Half-life is 3-7 hours. It is an extended-release preparation of metoprolol that yields a sustained and controlled release of the medication, permitting once-daily dosing and better compliance in patients. It primarily exerts its effect by inhibiting beta-1 adrenergic receptors in the heart, thus decreasing heart rate, cardiac output, and blood pressure. This mechanism assists in reducing the workload and oxygen requirement of the heart, thus being useful in preventing chest pain and managing blood pressure.

Metoprolol succinate is also commonly used in the treatment of chronic heart failure with reduced ejection fraction, in which it has been demonstrated to enhance survival and decrease hospitalizations. The medication is generally well tolerated, although side effects, including fatigue, dizziness, and bradycardia, are possible. It is recommended that treatment be initiated under medical supervision, particularly in patients with asthma, diabetes, or pre-existing conduction disturbances.

Gastro-retentive drug delivery systems (GRDDS) are novel oral drug delivery systems aimed at extending the stomach retention time of a dosage form. By staying in the gastric condition for a longer duration, these systems increase the bioavailability of drugs that are absorbed mainly in the stomach or upper small intestine. GRDDS may employ several mechanisms, like flotation, swelling, mucoadhesion, or high density, to gain extended gastric residence. Such systems are especially beneficial for drugs with limited absorption windows or unstable or poorly soluble drugs in intestinal fluids, thus providing enhanced therapeutic efficacy.

MATERIALS AND METHODS:

Materials: Metoprolol Succinate received as a gift sample from ‘Zeneka Healthcare. Others excipients such as HPMC, Magnesium stearate, talc was obtained from Loba Chemie Pvt. Limited. Carbopol 940, Calcium carbonate, SSG, Sodium stearyl fumarate was obtained from Nice Chemical Pvt. Ltd.

Methodology: At first weighed all the ingredients accordingly (Metoprolol succinate, Carbopol 940, Calcium carbonate, Hydroxypropyl methylcellulose, Sodium Starch Glycolate, Magnesium Stearate, Talc, Sodium stearyl fumarate). After that Sieve mess no 84# All are mixed in a double-cone blender. Then the granules were ready for compression. Tablets were done in MINIPRESS 8 STATION by the Direct compression method.

Sr. no	Ingredients	F1	F2	F3	F4	F5
		Mg per tablet				
1	Metoprolol succinate	12.5	12.5	12.5	12.5	12.5
2	Carbopol-940	100	120	130	128	150
3	Calcium carbonate	80	70	70	60	40
4	Hydroxypropyl methylcellulose	90	80	70	80	80
5	Sodium starch glycolate	30	30	30	30	30
6	Magnesium stearate	5	5	5	3	3
7	Talc	12.5	12.5	12.5	6.20	6.20

8	Sodium stearyl fumarate	-	-		10	8
9	Sodium benzoate	-	-		0.3	0.3
Total		330	330	330	330	330

Table 1: Formulation Batches of Metoprolol Succinate Floating Tablets

PREFORMULATION STUDIES:

To create stable, secure, and efficient dosage forms, pre-formulation is a stage of the research and development process where formulation describes the mechanical, chemical, and physical characteristics of novel therapeutic compounds.

PREPARATION OF STANDARD GRAPH:

A pure drug sample of Metoprolol Succinate was taken in the volumetric flask of 10ml capacity and the volume was made up with 0.1N HCL at pH 1. The stock solution was prepared using 10 mg/10 mL, equivalent to 1000 µg/ml. From 1000 µg/ml take 1 ml and make up to 10 ml, i.e., equivalent to 100 µg/ml. From 100 µg/ml take 1 ml, make up to 10 ml, i.e., equivalent to 10 µg/ml. From 10 µg/ml take 1 ml, make up to 5 ml, i.e., equivalent to 1µg/ml. Thus, different Concentrations of 2 µg/ml, 4 µg/ml, 6 µg/ml, 8 µg/ml, 10 µg/ml, and 12 µg/ml were prepared, and absorbance was taken at 274 nm.

Table 2: Standard Graph of Metoprolol Succinate

Concentration (µg/ml)	Absorbance
0	0
2	0.1109
4	0.2161
6	0.3173
8	0.4196
10	0.522
12	0.611

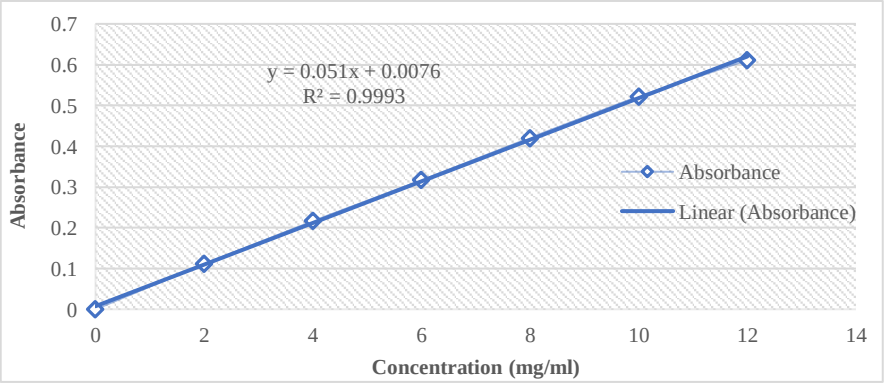

Fig. 1: Standard Calibration Curve of Metoprolol Succinate

FT-IR SPECTRUM OF METOPROLOL SUCCINATE:

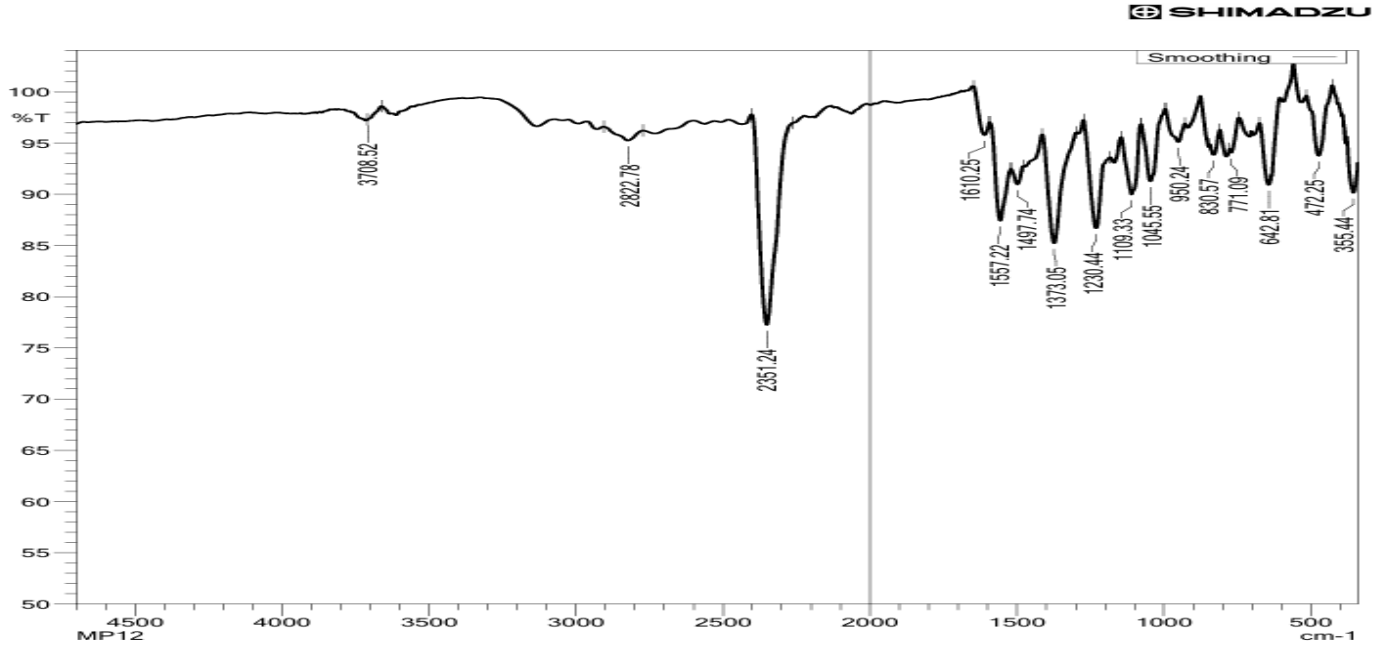

Fig. 2: FT-IR spectrum of Metoprolol Succinate

Sr.no	Reference Peak Wavenumber (cm-1)	Observed Peak Wavenumber (cm-1)	Functional Group
1	800-1200	830.57, 950.24, 1045.55, 1109.33,	C-C stretching Medium weak
2	1300-1500	1373.05, 1497.74,	C-H Bend in plane medium strong
3	900-1300	950.24, 1045.55, 1109.33, 1230.44	C-O Stretching Medium strong
4	1500-1700	1557.22, 1610.25,	N-H Bending medium
5	700- 900	771.09, 830.57,	N-H Rocking strong medium

Table 3: IR Interpretation of Metoprolol Succinate

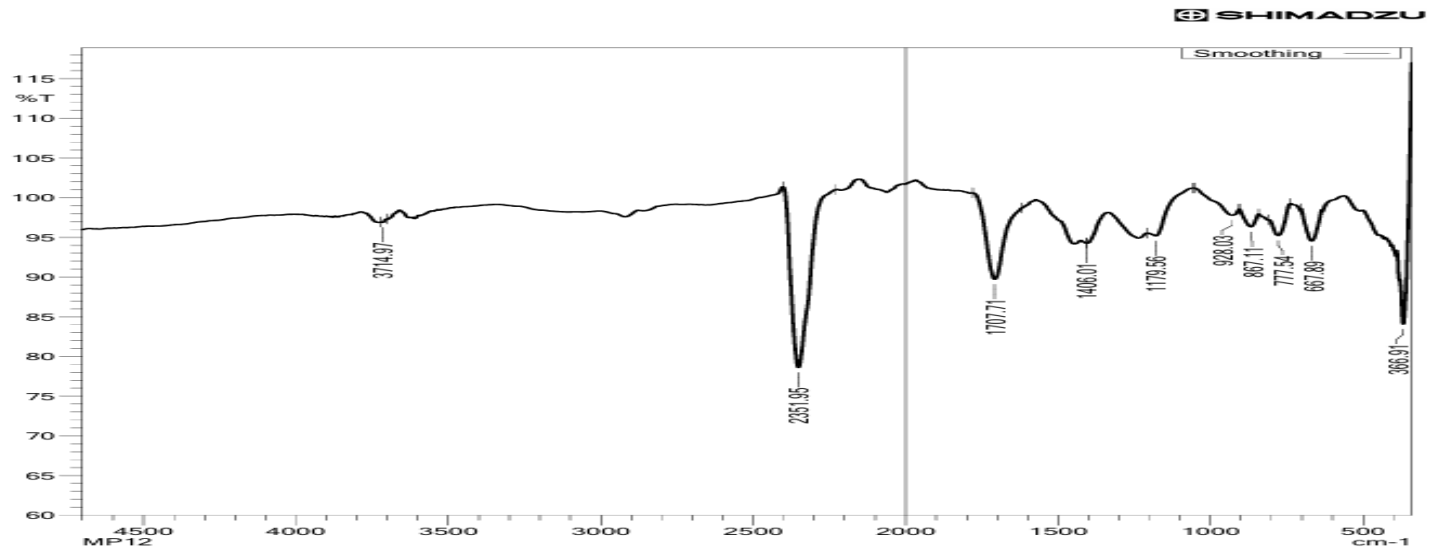

Fig. 3: FT-IR Spectrum of Metoprolol Succinate + Excipients

Sr.no	Reference Peak Wavenumber (cm-1)	Observed Peak Wavenumber (cm-1)	Functional Group
1	800-1200	867.11,928.03,1179.56	C-C stretching Medium weak
2	1300-1500	1406.01	C-H Bend in plane medium strong
3	700-900	777.54,867.11	N-H Rocking strong medium
4	900-1300	928.03,1179.56	C-O Stretching Medium strong

Table 4: IR Interpretation of Metoprolol Succinate + Excipients

The drug excipient compatibility study valley compares to IR spectra of Metoprolol Succinate; it shows no chemical reactions between drug excipient compatibility and Metoprolol Succinate. It was found that there is no interaction between drug and excipients.

BULK DENSITY:

Bulk density is defined as the mass of the material divided by the total volume occupied.

Bulk Density = Mass of the Material/ Total Bulk Volume

It is expressed as gm/ml.

Practical Observation:

Weight of Powder = 10g

Volume = 19 ml Bulk

Density = 10/19

= 0.52 gm/ml

TAPPED DENSITY:

It is defined as the total mass of the material divided by the total tapped volume of the sample. Tapped Volume = Mass of the material/ Total tapped volume.

Practical Observation:

Several taps is 100

The weight of the powder is 10 g.

After tapping, the tapped volume of powder is 16 ml

Tapped Density = Weight of the powder/Tapped Volume

= 10/16

= 0.62 gm/ml

POWDER FLOW PROPERTIES:

According to the density, particle size, and shape, the powder flow properties can be classified as free-flowing and cohesive. Carr's Index, Hausner ratio, and Angle of repose the suitable indicators to measure the powder flow properties.

Angle of Repose:

The angle of repose of the powder blend was determined by the funnel method. The accurately weighed powder blend was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powder blend. The powder blend was allowed to flow through the funnel, Greely onto the surface. The diameter of the powder cone was measured, and the angle of repose was calculated using an equation.

Angle of Repose (θ) = tan-1 (h/r) Where,

θ = Angle of Repose h = Height of the pile r = Radius

Practical Observation:

(θ) = tan-1 (h/r)

Height (h) = 2cm Radius(r) = 4

= tan-1 (2/4) = 25.56

Compressibility Index/ Carr's Index:

It is the indicator of the compressibility of a powder of granules. It can be calculated by the formula: Carr's Index (%) = (Tapped Density-Bulk density)/Tapped Density x 100

Practical Observation:

Carr's Index (%) = [(Tapped Density-Bulk density)/Tapped Density] x 100

= [(0.62-0.52)/0.62] x 100

=16 %

Hausner Ratio:

Number that correlated to the flow ability of a powder or granules material can be calculated as; Hausner Ratio = Tapped Density/Bulk Density.

Practical Observation:

Hausner ratio = Tapped density/Bulk density

= 0.62/0.52

= 1.19

FLOW PROPERTY	ANGLE OF REPOSE	COMPRESSIBILITY INDEX	HAUSNRES RATIO
Excellent	25-30	5-15	1.00-1.11
Good	31-35	12-16	1.12-1.18
Fair	36-40	18-21	1.19-1.25
Passable	41-45	23-35	1.26-1.34
Poor	46-55	33-38	1.35-1.45

Table 5: Value of Powder flow properties

RESULTS:

After formulating the Metoprolol Succinate floating tablets, we got the following results:

General Appearance: Bi-concave

Colour: White

Odour: Odourless

Taste: Bitter

HARDNESS: Tablets' resistance to shipping or breakage under conditions of storage, transportation, and handling before use, based on their hardness. The hardness of every batch of tablets was tested by a Monsanto hardness tester. The hardness was recorded in the units of kg/cm²; 6 tablets were selected randomly and tested for hardness: the mean hardness of 6 determinations was measured.

TABLET THICKNESS: The thickness of the tablet is determined by an electronic Vernier caliper. Tablet thickness should be regulated within a ± 5% deviation of the reference value. Moreover, thickness should be regulated to allow packaging. Thickness in millimetres (mm) was determined separately for ten pre-weighed tablets with an electronic Vernier calliper. The average thickness and standard deviation were indicated.

FRIABILITY: Friability specifically refers to the weight loss of tablets in the containers caused by fines removal from the tablet surface. Friability tends to indicate poor tablet component cohesion. 10 tablets were weighed, and the initial weight of such tablets was noted and put in the Roche friabilator and rotated at 25 rpm for 100 revolutions. Tablets were then taken out of the friabilator, and fines were weighed again, and the weight was recorded. Percentage friability was determined by employing the formula

% Friability = Weight initial- Weight final /Weight initial *100

WEIGHT VARIATION: Twenty tablets were randomly selected, and the average weight was determined. The individual tablets were weighed, and the percent deviation from the average was calculated.

As per IP, the Weigh variation Table:

Serial Number	Average weight of tablet(mg)	Maximum % weight variation allowed
1	≤80 mg	10
2	>80 mg – 250 mg	7.5
3	<250mg	5

Table 6: As per IP, the Weigh variation Range

DRUG CONTENT FOR FLOATING TABLET OF METOPROLOL SUCCINATE: 10 tablets of each preparation were weighed and crushed in a mortar and ground into powder. An amount of powder equivalent to 12.5mg of Metoprolol Succinate was weighed accurately and transferred to a 100 ml volumetric flask, and 0.1N HCl solution was added to it and shaken well. It was made up to a volume of 100 ml and filtered. Dilute the resulting solution to 10 mL with 0.1N HCl solution. Absorbance of the resulting solution was quantified at 274 nm via a UV-visible spectrophotometer.

SWELLING INDEX: The degree of swelling can be quantified in terms of % weight gain by the tablet. Swelling studies were conducted for formulations, and one tablet from every formula was weighed separately and kept isolated in a petri dish with 15 mL of 0.1 N HCl. The tablets were taken out of the petri dish after 24 hrs, and the surface excess liquid was eliminated carefully using tissue paper.

Swelling Index = (W2-W1) /W1 ×100

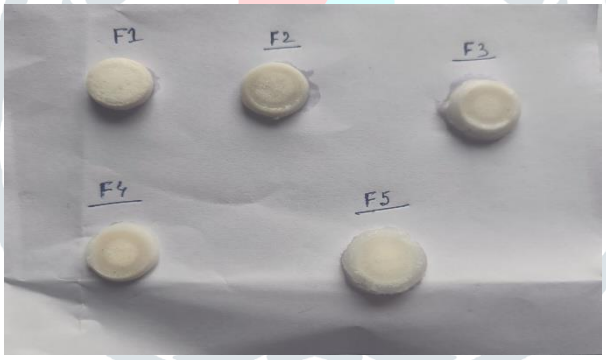

Fig. 4: Swollen tablet after 24 hrs.

IN-VITRO BUOYANCY DETERMINATION: Buoyancy Floating Test was conducted by putting tablets was put in a 100ml beaker with 0.IN HCl as the dissolution medium at 37 °C. The time taken by the tablet to float to the surface was found to be the total floating time.

Fig. 5: Buoyancy Determination of Floating Tablet

ACCELERATED STABILITY STUDIES:

Faster stabilization as part of the formal stability testing regimen, experiments were set up to hasten the rate of chemical degradation and physical transformation of a medicine by using accelerated storage conditions for 3-, 6-, 9-, and 12-months duration at a particular temperature, humidity, and light. Such testing allows pharmaceutical firms to assess a drug's long-term stability for a brief period under conditions like high temperatures, high humidity, and light exposure. Rapid pharmaceutical businesses perform stability studies to ascertain the expiration date of products and quality issues. The prepared formulation of Metoprolol Succinate of Floating tablets is kept in a glass container with parafilm at temp 40º±2ºCand a Relative humidity of 75±5% for 3 months. Samples were collected at one-month intervals for drug content estimation, and observed that the formulation was stable no physical and chemical changes occurring.

Formula Coad	Thickness (mm)	Hardness Kg/cm2	Friability (%)	Weight Variation	Swelling Index (%)	Drug Content (%)	Total Floating time (hr.)
F1	4.45	2	0.61	passed	110	96.32	10
F2	4.20	2.20	0.42	passed	128	97.51	12
F3	4.80	1.80	0.64	passed	147	97.69	14
F4	4.50	2	0.53	passed	152	98.32	14
F5	4.40	2.40	0.60	passed	125	98.64	16

Table 7: EVALUATION OF FLOATING TABLETS OF METOPROLOL SUCCINATE (POST COMPRESSION STUDIES)

IN-VITRO DISSOLUTION STUDY FOR FLOATING TABLETS:

In vitro release studies of the drug were performed on the USP Type II Dissolution test apparatus (Electro lab Model TDT-08L) at a paddle speed of 50 rpm. The dissolution was done in 900 ml of 0.1N HCl at 37± 0.5°C. The tablet of Metoprolol Succinate was weighed in the dissolution apparatus vessel, and the paddle was rotated at 50 rpm. 5 ml sample was drawn at a pre-determined time interval, and an equal volume of fresh dissolution fluid equilibrated at the same temperature was added, and the sample was suitably diluted with dissolution medium. The solution was filtered through Whatmann filter paper. The filtrate was scanned with a UV-Visible spectrophotometer.

TIME (hr)	CUMULATIVE PERCENTAGE DRUG RELEASE (%)				
	F1	F2	F3	F4	F5
0	0	0	0	0	0
1	5.25	2.17	6.31	6.98	4.31
2	9.76	8.04	11.12	16.25	9.12
3	17.51	16.23	18.06	30.59	16.06
4	25.64	20.34	26.34	41.46	24.34
5	35.47	30.12	34.97	54.73	32.97
6	43.91	41.23	43.83	62.16	41.83
7	54.38	48.34	52.84	71.61	50.84
8	62.85	57.67	60.24	76.58	58.24
9	74.15	64.38	68.83	80.92	66.83
10	83.62	73.92	77.62	85.38	75.62
11	88.83	80.67	85.3	89.77	83.3
12	90.6	84.1	91.09	91.06	92.63

Table 8: Invitro Drug Release Study

Cumulative % drug Release F1-F5

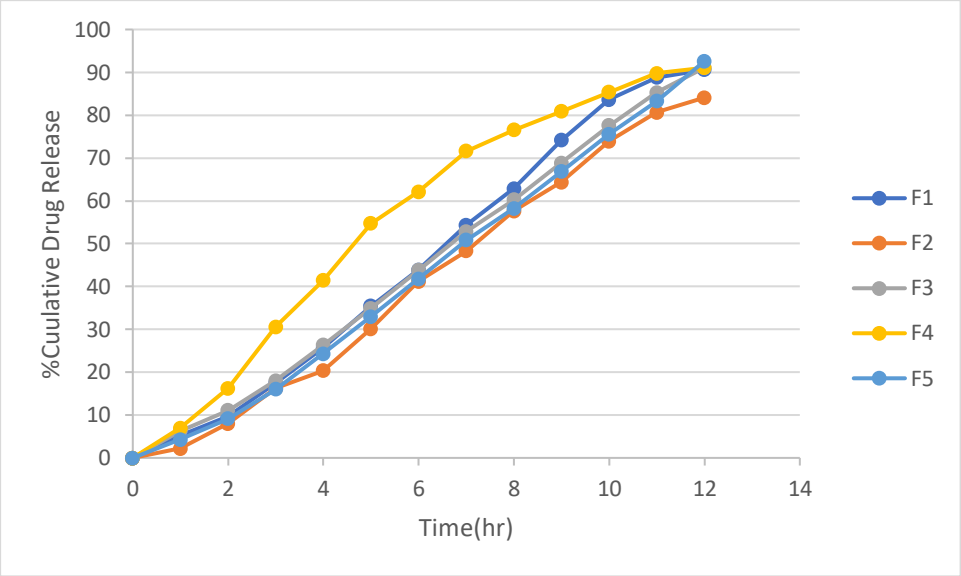

Fig.6: In-Vitro Drug Released Study

CONCLUSION: The current research effectively developed and tested Metoprolol Succinate floating tablets with different polymers and gas-generating agents to ensure prolonged gastric residence and controlled drug release. The optimized formulation exhibited satisfactory floating behaviour with a floating lag time of below 1 minute and total floating time of over 16 hours. In-vitro drug release studies indicated a sustained release pattern according to suggesting diffusion-controlled release. The use of hydrophilic polymers (e.g., HPMC, Carbopol) was successful in maintaining matrix integrity and buoyancy while controlling the rate of drug release. The floating drug delivery system improved gastric retention of Metoprolol Succinate, which could enhance its bioavailability and therapeutic effect by sustaining drug concentration within the absorption window for a longer duration. In summary, the optimized floating tablets represent an encouraging gastro-retentive delivery method for Metoprolol Succinate, calling for further in-vivo work to validate its clinical efficacy and performance.

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