International Journal of Current Advanced Research
ISSN: O: 2319-6475, ISSN: P: 2319-6505, Impact Factor: 6.614
Available Online at www.journalijcar.org
Volume 8; Issue 05 (C); May 2019; Page No.18717-18727
DOI: http://dx.doi.org/10.24327/ijcar.2019.18727.3587

Research Article

FORMULATION AND DEVLOPMENT OF ORAL CONTROLLED RELEASE TABLET OF SUCRALFATE AND METOPROLOL SUCCINATE AS FLOATING DRUG DELIVERY SYSTEM

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A R T I C L E I N F O

Article History:
Received 4th February, 2019
Received in revised form 25th March, 2019
Accepted 23rd April, 2019
Published online 28th May, 2019

Key words:
Sucralfate , Metoprolol Succinate,FDDS,Stomach ulcer , Hypertension, Pregnancy & lactation.

A B S T R A C T

The present research deals with formulation and development of 150 mg oral controlled release tablet (Bi-Layered Floating Tablet) containing 100 mg of Ulcer protective Sucralfate as immediate release layer and 50 mg of Antihypertensive Metoprolol Succinate as floating sustained release layer having tablet wt 500 mg. Drug - exipients compatibility study, preparation and evaluation of 10 formulation of Sucralfate and 10 formulations of Metoprolol succinate is done and best formulations are selected. Then Bi-Layered floating tablet is prepared and evaluated. By in vitro study it is found that In presence of maximum % of Sodium bicarbonate, Magnesium oxide, and Sodium CMC the Sucralfate layer (SF9) produce disintegration time 0.58 ± 0.075 minutes and drug content 99.23 %.in stomach medium and In presence of maximum % of Metoloze, Acrilic acid, and Aerosil the Metoprolol succinate layer (MSF10) produce FLT 12sec, TFT >24 hours.in upper intestinal phase. Then Bi Layered floating tablet (SFMS) is compressed having tablet weight 500 mg with formulations (SF9 + MSF10) . In vitro evaluation of SFMS produce DT 2.04± 0.157 min ,FLT 10sec,TFT >24hrs,and drug content 99.98% . So it is confirmed that the formulation (SF9 +MSF10) produce better Floating Drug Delivery system.

INTRODUCTION

Technologies used in oral drug delivery of the controlled release dosage forms (Bi Layered Floating Tablet) are one of the leading area of the science participating in health care of human beings[1].The development of oral controlled release system has been a challenge to formulation scientist due to their inability to restrain and localise the system at targeted area of GI tract. The oral controlled drug delivery system aim to maintain plasma concentration of drug within the therapeutic window for a longer period of time, thereby to ensure to sustained therapeutic action,[2]

Peptic ulceration is an uncommon cause of death in pregnant women. The mortality rates in these patients are high, particularly in those with perforated ulcer; in many cases the foetal outcome appears to be due to late diagnosis.[3]

Hypertension during pregnancy is an important cause of morbidity and mortality in both the mother and her offspring during the prenatal period. It effect on the mother's vascular health and extend for many years after the pregnancy. Hypertension during pregnancy was associated with increased coronary heart disease and stroke incidence in middle age.[4]

Sucralfate has the theoretical advantages that it does not favour colonisation of the stomach with colonic flora; it can be implemented particularly in patients with gastric ulcer and atrophic gastritis.

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Since maintenance treatment with either Sucralfate or antisecrotory agents reduces the recurrence rate of gastric ulcer. So Sucralfate is considered as clinically relevant.[5] It can be administrated in empty stomach max 1 gm before 1 hr of mill in case of acidity in pregnancy and lactation[6]. It provide surface protein at ulcer base and act as physical barrier preventing acid.

Metoprolol succinate [7] is selective β-1 blocker. applicable for mild to moderate essential hypertension,angina pectroris, myocardial infraction. It can provide the sustained action on blood pressure over 24 hours. So it is an effective drug to treat essential hypertension.7 It have low risk of adverse effect on uterus. The starting dose is 100 mg once a day and maintenance dose 200 mg /day in empty stomach.

Both the drugs Sucralfate and Metoprol succinate can be implemented in combine form in empty stomach in period of pregnancy and lactation and they produce minor drug interaction[8]. So they can be implemented in pregnant mother as well as lactate mother suffering from pregnancy and lactation.

The objective of present research to develop a best formulation from 10 formulations of Sucralfate and 10 formulations of Metoprol succinate by various evaluation process[9] according to IP and accelerated stability study according to ICH guideline.Then it is formulated as 150 mg Bilayer floating tablet in which 100 mg Sucralfate act as immediate release layer and 50 mg Metoprolol Succinate act as sustained release layer having tablet wt 500 mg.

MATERIALS AND METHODS

According to different properties and uses of various exepients are taken in different ratios to formulate and optimize Bi-layered Floating Tablet of Sucralfate and Metoprolol Succinate.[T-1,T-2]

Composition of IR Sucralfate Tablets and floating SR Metoprolol Succinate tablets [T-3,T-4]

10 formulations of Sucralfate and 10 formulations of Metoprolol Succinate are prepared.

Drug-excipient compatibility studies [T-5,T-6]

Drug-Exipient compatibility study is done at 45^0C and 75% RH for a period of 90 Days. Drug – exipients 1:1 ratio were packed in 85mm HDPE bottles with an oxygen adsorbent, a molecular sieve and a desiccant containing silica gel with cotton as filler and made the compatible study.

Recovery of less compatible formulations

In SF2 by increasing the quantises of 3 mg of Magnesium Stearate and decreasing the quantities of 3 mg Aerosil,
In SF4 by increasing the quantises of 2 mg of Magnesium Stearate and decreasing the quantities of 2 mg Aerosil,
In SF7 by increasing the quantises of 3 mg of Magnesium Stearate and decreasing the quantities of 3 mg HPMC,
In MSF5 by increasing the quantises of 5 mg of Talc and decreasing the quantities of 5 mg Ethyl cellulose,
InMSF7 by increasing the quantises of 5 mg of Talc and decreasing the quantities of 5 mg Ethyl Cellulose,
InMSF8 by increasing the quantises of 5 mg of Talc and decreasing the quantities of 5 mg Ethyl cellulose.

Final formulation of IR Sucralfate Tablets and floating SR Metoprolol Succinate tablets [T-7,T-8]

Finally 10 formulations of Sucralfate and 10 formulations of Metoprolol Succinate are prepared.

Preformulation study [10]

The preformulation studies like flow properties, solubility were determined.

Flow properties are studied of Sucralfate and Metoprolol succinate formulations. [T-9,T-10]

The following flow properties of the lubricated granules were evaluated.

Angle of Repose (Θ): It was determined by using a funnel whose tip was fixed at a constant height (H) of 2.5cm from horizontal surface. The granules and the powder were passed separately through the funnel until the tip of the conical pile touches the tip of the funnel. The radius of the base of the conical pile is measured as R (cm). It is determined with the formula;
Angle of repose (θ) = Tan^{-1} (height of pile /radius of pile).

Angle of Repose	Powder flow
< 25	Excellent
25-30	Good
30-40	Passable
< 40	Very poor

Bulk density and Tapped density (g/ml)

The previously weighed pure drug or granules (W) were placed separately into a graduated measuring cylinder and the initial (bulk) volume (V_B) was noted. It was placed in the tapped density tester USP and subjected to constant tapping at a rate of 200drops/min until the difference between the initial and final volumes should be less than 2%. It was recorded as the final (tapped) volume (V_T) and various flow properties were calculated with the following formulae.

Bulk density, $\rho B = \frac{W}{VB}$ Tapped density, $\rho T = \frac{W}{VT}$

Compressibility Index

It was calculated by using the following formula

Carr's Index or Compressibility Index (CI) = $1-\frac{\rho B}{\rho T} * 100$

The CI value below 15% indicates good flow of the powder and above 30% indicates poor flow property of the powder.

Hausner's Ratio: It is calculated by the following formula;
Hausner's Ratio= $\frac{\rho T}{\rho B}$

The Hausner's ratio below 1.25 indicates good flow property and above 1.25 indicates poor flow property of the powder.

***Preparation of granules*:**[11]

Preparation of Sucralfate granules

The10 formulations of Sucralfate IR tablets were prepared by wet granulation method**.** The composition of the tablet is mentioned in[T-7.] The required ingredients were weighed accurately and passed through 40 mesh. The sieved materials were then mixed well in a poly bag for about 30 minutes. The surfactants, Alginic acid were dissolved in cold and hot water respectively to use as granulating fluid. To moisten the blend, either water or surfactant solution was used as granulating fluid. The wet mass was granulated in RMG granulator. The granules were then dried in a Retsch rapid dryer at 60^0C for about 60 minutes until the % LOD becomes less than 3%. The dried granules were then passed through 40 mesh and then lubricated by mixing with the lubricant (which was previously passed through 60 mesh) in a polybag for about 15 minutes. The flow properties of the lubricated granules were determined.

Preparation of Metoprolol Succinate Granules

The Metoprolol Succinate floating SR granules were prepared by wet granulation method. The composition of the tablets is given in [T-8.] The drug and polymer which were previously passed through 40 mesh were mixed thoroughly in a polybag for 20 minutes. The blend was moistened with granulating fluid i.e., water and IPA (1:9 parts). The wet mass was passed through 24 mesh and then dried in a tray dryer at 50^0C for about 50 minutes until the % LOD becomes less than 2%. The dried granules were passed through 30 mesh and mixed with sodium bicarbonate in a polybag for 10 minutes. To this talc (previously passed through 60mesh) was added and mixed well for 10 minutes. The flow properties of the lubricated granules were evaluated.

Preparation of Tablet [13]

Preparation of Sucralfate (IR) layer in BIlayer Floating Tablet

The lubricated granules were then compressed by using 16 station tablet compression machine (CADMACH) with 7 mm plane round shaped punches. 10 formulations of Sucarlfate tablet are made of different compositions**.**

Preparation of Metoprolol Succinate (SR) tablet

The lubricated granules were compressed by 16 station tablet compression machine (CADMACH) with 13.1mm round concave punches. The 10 formulations of different compositions are made

The Post comprisal parameters of formulations of Sucralfate and Metoprol Succinate. [T-11,T-12]

According to IP the Post comprisal parameters like hardness, thickness,% friability, disintegration time were evaluated for all the prepared tablets. The drug content was determined for all the batches. Dissolution studies were conducted for all formulations.

Weight Variation

Twenty tablets were collected randomly and the average weight and individual weight was calculated. The % weight variation was calculated with the following formula.
%Weight variation= Average weight-individual weight/individual weight x100

Thickness

The thickness of the ten tablets was measured in mm by using Vernier calipers.

Hardness

The hardness of the ten tablets was measured by using Varian V K200 Tablet Hardness Testerand is given in the units of KP.

Friability

Ten tablets were carefully dedusted prior to testing and weighed accurately (Wo). The tablets were placed in the drum of Roche Friabilator (USP). The drum was rotated for 100 times at a speed of 25rpm. The tablets were collected, re-dedusted and accurately weighed (W1). It is calculated form the following formula;

$$\% \text{ Friability} = 1 - \frac{W1}{W0} * 100$$

Disintegration Test

The disintegration study was performed for Sucralfate tablets by using disintegration apparatus Thermonik DT Tester (USP). For this water was used as the disintegration medium. 6 tablets were placed in 6 tubes of the disintegration apparatus. The time (min) taken for the tablets to disintegrate was noted.

Floating lag time (FLT)

The MS tablets were placed in a beaker containing 250ml of 0.1N HCl and the time (sec) required to float the tablet was observed and recorded as FLT.

Total floating time (TFT)

The time (hr) up to which the MS tablet remains buoyant was noted and recorded as TFT.

Determination of drug content of Sucralfate tablets: [T-11]

Ten SF tablets were weighed accurately and then crushed well in a clean motor and pestle. The powder equivalent to 25mg of the drug was weighed (Ws) and then transferred to a 100ml volumetric flask. 50ml methanol was added and sonicated for 5 minutes at 27^0C. Then the volume was made up to 100ml using methanol (V4). From this 4ml (V5) was transferred to a 100ml volumetric flask and the volume was made up to 100ml (V6) with 0.1N HCl (pH 1.2). The flask was agitated for 5 minutes and then the sample was analyzed for drug content at 281nm using UV Spectrophotometer. The drug content was calculated using the following formula.

$$\textbf{\% Drug Content} = \frac{AS}{AS} * \frac{W}{V1} * \frac{V2}{V3} * \frac{V4}{WS} * \frac{V6}{V5} * \frac{AW}{L} * P$$

Where,
AS= Test absorbance
AS= Standard Absorbance
W= Weight of standard drug (25mg)
V1= Volume of solvent added to standard stock solution (100ml)
V2, V3= Dilution of the standard stock solution (4ml of stock solution diluted to 100ml with solvent)
AW= Average weight of the tablet (mg)
L= Label claim of the drug (10mg)
P = Potency of sucralfate (91.4%).

Determination of drug content of Metoprolol Succinate tablets: [T-12]

Ten MS tablets were weighed and crushed in a motor with pestle. The crushed powder equivalent to 100mg of MS (WS) was weighed accurately and transferred to a clean, dried 100ml volumetric flask. 50 ml of 0.1N HCl was added and agitated vigorously for 10 minutes and sonicated for 4 hours. The final volume was made up to 100ml (V4) using 0.1N HCl and agitated for 5 minutes. A portion of it was centrifuged at 300 rpm for 10 minutes. The centrifuged sample was filtered through 0.45µm whatmann filter paper. 2 ml (V5) of the filtered sample was pipetted out and transferred to a 100ml volumetric flask and the volume was made up to 100ml (V6) with 0.1N HCl and the flask was shaked for 5 minutes. The sample was then analyzed for the drug content at 233nm using UV Spectrophotometer. The drug content was calculated using the following formula.

$$\textbf{\% Drug Content} = \frac{AS}{AS} * \frac{W}{V1} * \frac{V2}{V3} * \frac{V4}{WS} * \frac{V6}{V5} * \frac{AW}{L} * P$$

AS= Test absorbance
AS= Standard Absorbance
W= Weight of standard drug (100mg)
V1= Volume of solvent added to standard stock solution (100ml)
V2, V3= Dilution of the standard stock solution (2ml of stock solution diluted to 100ml with solvent)
Aw= Average weight of the tablet (mg)
L= Label claim of the drug (375mg)
P = Potency of metoprolol succinate (99.83%).

Determination of swelling index of Metoprolol Succinate tablets: [T-13]

The previously weighed (W1) tablet was placed in USP apparatus type-I which was immersed in a bowel containing 900ml of 0.1N HCl and maintained at 37 ± 0.2^0C. The tablets were removed from the basket at regular intervals of time (up

to 8hrs with 1 hr interval) and placed on a blotting paper to remove the excess medium . The tablet was reweighed (W2). The studies were repeated for all formulations in triplicate. The swelling index was calculated as follows:

Swelling Index = W2-W1/W1 x 100

Acclerated stability study of Sucralfate tablets [T-14]

10 Tablets of Sucralfate tablets were subjected to accelerated stability studies[12] at 45^0C and 75% RH for a period of 90 Days. The tablets of SFMS were packed in 85mm HDPE bottles with an oxygen adsorbent, a molecular sieve and a desiccant containing silica gel with cotton as filler. The tablets were withdrawn after the stability period, and evaluated for physical and chemical changes.

Acclerated stability study of Metoprolol Succinate tablets [T-15]

10 Tablets of Metoprolol Succinate tablets were subjected to accelerated stability studies at 45^0C and 75% RH for a period of 90 Days. The tablets of SFMS were packed in 85mm HDPE bottles with an oxygen adsorbent, a molecular sieve and a desiccant containing silica gel with cotton as filler. The tablets were withdrawn after the stability period, and evaluated for physical and chemical changes.

Selection of best formulation of Sucralfate and Metoprolol Succinate. [T-16,T-17]

According to Accelerated stability study of lubricated granules and Post compressional parameters and Accelerated stability study of compressed tablets one formulation of Sucralfate (SF9) and one formulation of Metoprolol succinate(MSF10) is selected.

Preparation of Bi-layered tablets of SFMS.

Sucralfate layer and Metoprolol Succinate layer, Bilayered Floating tablets were prepared. The Bi-Layered tablets of Sucralfate and Metoprolol Succinate (SFMS) were compressed using 13.1mm round concave punches using a Bi-Layered Tablet Compression Machine. The granules of Metoprolol Succinate were placed first and pre-compressed with slight hardness of about 4-5KP. Then the granules of Sucralfate were placed and compressed with a final hardness of about 12-14 KP. The compression of Bi-Layered Tablet is based upon Composition of optimized Sucralfate layer and composition of optimized Metoprolol Succinate layer ,

The post compressional parameters of SFMS tablets . [T-18]

The post compressial parameters ; Average weight, Thickness, Hardness,% friability, FLT, TFT, DT of Sucralfate Layer is determined**.**

Acclerated stability study of SFMS bi layered tablets [T-19,T-20]

10 Tablets of SFMS Bi-layered tablets were subjected to accelerated stability studies[12] at 45^0C and 75% RH for a period of 90 Days. The tablets of SFMS were packed in 85mm HDPE bottles with an oxygen adsorbent, a molecular sieve and a desiccant containing silica gel with cotton as filler. The tablets were withdrawn after the stability period, and evaluated for physical properties like weight variation, thickness, hardness, % friability, disintegration time of SF layer, FLT and TFT of MS layer and in vitro drug release studies**.**

Release kinetic profile of Sucralfate [T-21,T-22]

The cumulative drug release study of Sucralfate in pH 6.8 phosphate buffer at 281 nm is done and graph is plotted. The cumulative drug release study of Sucralfate in0.1 N HCl at 281 nm is done and graph is plotted.

The cumulative drug release study of Metoprolol Succinate in 0.1 N HCl at 233 nm is done and graph is plotted.[Fig-1,Fig-2]

Release kinetic profile of Metoprolol Succinate[T-23]

The best fit with the highest determination R^2 coefficients was shown by both zero order models and Higuchi model followed by Korsemeyerpeppas which indicate the drug release via diffusion mechanism. Zero-order rate equations, which describe the system where release rate is independent of the concentration of the dissolved species. The Korsemeyerpeppas equation is used to analyze the release of pharmaceutical polymeric dosage forms,

From the result it was confirmed that all the formulations are following higuchi model which indicate the drug release via diffusion mechanism. The slope value fromkorsemeyer plots confirmed that the formulations are following Fickian diffusion.[Fig-3,Fig4,Fig5,Fig6,Fig7]

RESULT AND DISSUCITION

Composition of Sucralfate and Metoprolol Succinate formulations [T-3,T-4]

The 10 formulations of Sucralfate and 10 formulations Metoprolol Succinate are composed by taking various ingredients of different ratios.

Drug-excipient compatibility studies [T-5,T-6]

The formulations ; SF2,SF4,SF7 produce less compatibility and MSF5,MSF7,MSF8 produce less compatibility by producing less flowibility after 90 days of accelerated studies.

Composition of Sucralfate and Metoprolol Succinate formulations after recovery of incompatibility. [T-7,T-8]

The final formulations of Sucralfate and final formulations Metoprolol Succinate are composed by changing ratios of various ingredients of less compatible formulations.

Preformulation Studies

Flow Proreties of lubricated Granules[T-9,T-10]

The lubricated granules obtained from wet granulation of Sucralfate and Metoprolol Succinate with different excipients are evaluated which produce better flow properties .

Evaluation of Tablets

The Post compressional parameters of Sucralfate Tablets [:T-11]

It shows SF9 produce better result ; avrage weight 205.2±0.500 mg, thickness 3.20±0.010mm, heardness 5.45±0.109kg/cm^2,% friability 0.292, Disintigration time-0.98±0.075, % drug content-99.23%

The Post compressional parameters of Metoprolol Succinate Tablets **:** [T-12]

It shows MSF10 produce better result ; avrage weight 295.8±0.431mg, thickness 3.52±0.005mm, heard ness 7.98±0.004 kg/cm^2,% friability 0.179, % drug content-99.59%,

Buoyancy study of Metoprolol Succinate

In vitro Buoyancy study of MSF10 shows Floating Lag Time 12 Sec and Total FloatingTime >24 hours.

Swelling index of Metoprolol Succinate: [T-13]

Swelling index values observed from MSF2 shows 238.91.% at 8 hours.

Drug content of Sucralfate and Metoprolol Succinate Tablets

Drug content of each formulations of Sucralfate and Metoprolol Succinate Tablets shows appx more than 98% of drug release.

Acclerated stability study of Sucralfate and Metoprolol Succinate Tablets

Accelerated stability shows there is some negligible change in colour or some black spots were observed in some formulations .So we except it will not produce more impact on optimization of further formulations and it may be recoverable on further optimization.[T-14.T-15]

Selection of best formulation of Sucralfate and Metoprolol Succinate

According to Accelerated stability study of lubricated granules and post compressional parameters and Accelerated stability study of compressed tablets SF9 and MSF10 is selected.[T-16,T-17]

Post compressional parameters of SFMS Bilayered Floating Tablet . [T-18]

After optimization of Sucralfate and Metoprolol Succinate formulations The Bilayered Floating Tablet is prepared and post compressional parameters[14] are studied and found that the Disintigration Time of Sucralfate is 2.04±0.157 in Stomach medium and F.L.T of Metoproplol Succinate is 10 sec and T.F.T is >24 hours and Drug release 99.98%

Accelerated Stability study and in vitro evaluation of SFMS Bilayered Floating Tablet at different time period [T-19]

Physical properties like weight variation, thickness, hardness, % friability, disintegration time of SF layer, FLT and TFT of Bilayed floating tablet shows near about equivalent parameters as initial post compresional parameters**.** Disintigration Time of Sucralfate is 2.02±0.34 in Stomach medium and F.L.T of Metoproplol Succinate is 8.02 sec and T.F.T is >24 hours and drug release 99.56% after 90 days.

Release kinetic profile of Sucralfate [T-21,T-22Fig-1.Fig-2]

The cumulative drug release study of Sucralfate in pH 6.8 phosphate buffer at 281 nm produce absorbance 0.9153±0.0004 at concentration 25 µg/ml.and R^2 is 0.987.
The cumulative drug release study of Sucralfate in0.1 N HCl at 281 nm produce absorbance 0.8951±0.0004 at concentration 25 µg/ml.and R^2 is 0.912.

Release kinetic profile of Metoprolol Succinate: [T-23,Fig-3,Fig-4,Fig-5,Fig-6,Fig-7]

The cumulative drug release study of Metoprol succinate in0.1 N HCl at 233 nm produce absorbance 0.9152±0.0003 at concentration 25 µg/ml.and R^2 is 0.997.

The best fit with the highest determination R^2 coefficients was shown by zero order models which produce R^2 =0.084, First order plot produce R^2 =0.986, Higuchi model produce R^2 =0.982 and Pappas plot shows R^2 =0.988.

Table 1 Li st of excipients used for the preparation of Sucralfate layer.

SL. NO.	EXCIPIENT NAME	CATEGORY
1	Sodium CMC	Tablet Disintegrant
2	Calcium Phosphate	Tablet Filler/ Diluent
3	MCC	Tablet Filler/ Diluent
4	Sodium bicarbonate	Alkalizing Agent
5	Magnesium oxide	Alkalizing agent
6	Aerosil/ colloidal SiO2	Tablet Disintegrant
7	Hydroxy Propyl Methyl Cellulose	Tablet Binder
8	Sodiumlaurylsulfate	Solubilizer
9	Alginic Acid	Surfectants
10	Magnesium Stearate	Tablet lubricant
11	Sunset Yellow	Coloring agent
12	SLS	Surfectant

Table 2 List of excipients used for the preparation of Metoprolol Succinate

Sl.no	Excipient name	Category
1	Ethyl cellulose	Drug release retardant
2	Methocel K100 LV	Matrix former
3	Acrilic acid	Matrix Former
4	Xanthan gum	Swellable Polymer
5	Metoloze	Swellable Polymer
6	Polyox	Swellable polymer
7	Eudragit polymers	Swellable polymer
8	Aerosil/ colloidal SiO2	Anti-caking agent
9	Talc	Tablet Glidant
10	Isopropyl alcohol (IPA)	Solvent
11	Purified water	Granulating fluid
12	Sodium Bicarbonate	Alkalizing agent

Table 3 Composition of IR Sucralfate Tablets
IR-Immediate release.

	INGREDIENTS	QUANTITY PER TABLET IN MG									
		SF 1	**SF 2**	**SF 3**	**SF 4**	**SF 5**	**SF 6**	**SF 7**	**SF 8**	**SF 9**	**SF10**
1	Sucralfate	100	100	100	100	100	100	100	100	100	100
2	Sodium CMC	0	5.84	6,5	7.1	8	3.4	8.5	6	12.5	3.505
3	Calcium Phosphate	17.5	24.46	25.73	8.2	8.8	5.4	10.2	19.3	1.3	22.97
4	MCC	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
5	Sodium bicarbonate	90	85	80	90	90	85	90	85	90	80
6	Magnesium oxide	75	80	85	90	85	90	80	75	85	85
7	Aerosil/ colloidal SiO2	3.8	3	1	2	1	3	1	2	2	1
8	Hydroxy Propyl Methyl Cellulose	10	0	0	0	5	10	5	10	5	5
9	Sodiumlaurylsulfate	0	0	0	1	0.5	1.5	2	0.5	2.5	0
10	Alginic Acid	0	0	1.07	0	0	0	0	0	0	0.625
11	Magnesium Stearate	2.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
12	Sunset Yellow	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
13	SLS	0	0	0.2	0	0.2	0	0.5	0.5	0	0.2
	TOTAL	300	300	300	300	300	300	300	300	300	300

Table 4 Composition of floating SR Metoprolol Succinate tablets
SR-Sustained release.

SL. NO	INGREDIENTS	QUANTITY PER TABLET IN MG									
		MSF1	**MSF2**	**MSF3**	**MSF4**	**MSF5**	**MSF6**	**MSF7**	**MSF8**	**MSF9**	**MSF10**
1	Metoprolol Succinate	50	50	50	50	50	50	50	50	50	50
2	Ethyl cellulose	50	50	50	50	45	50	45	45	50	50
3	Xanthan Gum	50	-	-	-	50	-	-	-	50	-
4	Metoloze	-	50	-	-	-	50	-	-	-	50
6	Polyox	-	-	50	-	-	-	50	-	-	-
7	Eudragit	-	-	-	50	-	-	-	50	-	-
8	Methocel	25	-	25	-	25	-	25	-	25	-
8	Acrilic acid	-	25	-	25	-	25	-	25	-	25
9	Aerosil/ colloidal SiO2	15	15	15	15	15	15	15	15	15	15
10	Talc	5	5	5	5	10	5	10	10	5	5
11	Isopropyl alcohol (IPA)	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS
12	Purified water	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS
13	Sodium Bicarbonate	5	5	5	5	5	5	5	5	5	5
	TOTAL WEIGHT	200	200	200	200	200	200	200	200	200	200

Table 5 Drug exipient compatibility study of Sucralfate formulations

Granules	After 7 days	After 15 days	After 30 days	Aftrer 45Days	After 60Days	After 90Days	COMPATIBILITY
SF1	No Change	No Change	No Change	No Change	No Change	No change	Compatible
SF2	No Change	No Change	No Change	No Change	No Change	Less flowbility	Less compatible
SF3	No Change	No Change	No Change	No Change	No Change	No change	Compatible
SF4	No Change	No Change	No Change	No Change	No Change	Less flowbility	Less compatible
SF5	No Change	No Change	No Change	No Change	No Change	No change	Compatible
SF6	No Change	No Change	No Change	No Change	No Change	No change	Compatible
SF7	No Change	No Change	No Change	No Change	No Change	Less flowbility	Less compatible
SF8	No Change	No Change	No Change	No Change	No Change	No change	Compatible
SF9	No Change	No Change	No Change	No Change	No Change	No change	Compatible
SF10	No Change	No Change	No Change	No Change	No Change	No change	Compatible

Table 6 Drug exipient compatibility study of Metoprolol Succinate formulations

Granules	After 7 days	After 15 days	After 30 days	Aftrer 45 Days	After 60 Days	After 90Days	COMPATIBILITY
MSF1	No Change	No Change	No Change	No Change	No Change	No change	Compatible
MSF2	No Change	No Change	No Change	No Change	No Change	No change	Compatible
MSF3	No Change	No Change	No Change	No Change	No Change	No change	Compatible
MSF4	No Change	No Change	No Change	No Change	No Change	No change	Compatible
MSF5	No Change	No Change	No Change	No Change	No Change	Less flowbility	Less compatible
MSF6	No Change	No Change	No Change	No Change	No Change	No change	Compatible
MSF7	No Change	No Change	No Change	No Change	No Change	Less flowbility	Less compatible
MSF8	No Change	No Change	No Change	No Change	No Change	Less flowbility	Less compatible
MSF9	No Change	No Change	No Change	No Change	No Change	No change	Compatible
MSF10	No Change	No Change	No Change	No Change	No Change	No change	Compatible

Table 7 Final Composition of IR Sucralfate Tablets
IR-Immediate release.

	Ingredients	Quantity Per Tablet in mg									
		SF 1	**SF 2**	**SF 3**	**SF 4**	**SF 5**	**SF 6**	**SF 7**	**SF 8**	**SF 9**	**SF10**
1	Sucralfate	100	100	100	100	100	100	100	100	100	100
2	Sodium CMC	0	5.84	6.745	7.1	8	3.4	8.5	6	12.5	3.505
3	Calcium Phosphate	17.5	24.46	25.73	8.2	8.8	5.4	10.2	19.3	1.3	22.97
4	MCC	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
5	Sodium bicarbonate	90	85	80	90	90	85	90	85	90	80
6	Magnesium oxide	75	80	85	90	85	90	80	75	85	85
7	Aerosil/ colloidal SiO2	3.8	0	1	0	1	3	1	2	2	1
8	Hydroxy Propyl Methyl Cellulose	10	0	0	0	5	10	2	10	5	5
9	Sodiumlaurylsulfate	0	0	0	1	0.5	1.5	2	0.5	2.5	0
10	Alginic Acid	0	0	1.07	0	0	0	0	0	0	0.625
11	Magnesium Stearate	2.2	3.2	0.2	2.2	0.2	0.2	3.2	0.2	0.2	0.2
12	Sunset Yellow	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
13	SLS	0	0	0.2	0	0.2	0	0.5	0.5	0	0.2
	TOTAL	300	300	300	300	300	300	300	300	300	300

Table 8 Final Composition of floating SR Metoprolol Succinate tablets
SR-Sustained release.

Sl. No	Ingredients	Quantity Per Tablet In Mg									
		MSF1	**MSF2**	**MSF3**	**MSF4**	**MSF5**	**MSF6**	**MSF7**	**MSF8**	**MSF9**	**MSF10**
1	Metoprolol Succinate	50	50	50	50	50	50	50	50	50	**50**
2	Ethyl cellulose	50	50	50	50	45	50	45	45	50	**50**
3	Xanthan Gum	50	-	-	-	50	-	-	-	50	**-**
4	Metoloze	-	50	-	-	-	50	-	-	-	**50**
6	Polyox	-	-	50	-	-	-	50	-	-	**-**
7	Eudragit	-	-	-	50	-	-	-	50	-	**-**
8	Methocel	25	-	25	-	25	-	25	-	25	**-**
8	Acrilic acid	-	25	-	25	-	25	-	25	-	**25**
9	Aerosil/ colloidal SiO2	15	15	15	15	15	15	15	15	15	**15**
10	Talc	5	5	5	5	10	5	10	10	5	**5**
11	Isopropyl alcohol (IPA)	QS	QS	QS	QS	QS	QS	QS	QS	QS	**QS**
12	Purified water	QS	QS	QS	QS	QS	QS	QS	QS	QS	**QS**
13	Sodium Bicarbonate	5	5	5	5	5	5	5	5	5	**5**
	TOTAL WEIGHT	200	200	200	200	200	200	200	200	200	**200**

Table 9 Flow properties of lubricated granules of Sucralfate

Formulation Code	Angle of Repose (Θ)	Bulk Density (g/ml)	Tapped Density (g/ml)	Compressibility Index (%)	Hausner's Ratio	%LOD
SF1	24.64	0.510	0.619	26.20	1.314	2.13
SF2	23.71	0.528	0.655	21.31	1.248	2.86
SF3	26.92	0.546	0.694	21.33	1.254	2.68
SF4	25.43	0.454	0.547	17.17	1.186	2.26
SF5	26.13	0.503	0.629	20.03	1.264	2.28
SF6	25.52	0.506	0.634	20.19	1.257	2.74
SF7	26.19	0.502	0.609	17.57	1.229	2.78
SF8	26.33	0.526	0.676	22.25	1.229	2.92
SF9	26.23	0.501	0.615	18.54	1.310	2.73
SF10	26.28	0.500	0.627	20.25	1.263	2.78

Table 10 Flow properties of lubricated granules of Metoprolol Succinate

Formulation Code	Angle of Repose (Θ)	Bulk Density (g/ml)	Tapped Density (g/ml)	Compressibility Index (%)	Hausner's Ratio	%LOD
MSF1	28.54	0.298	0.489	27.59	1.392	1.84
MSF2	24.63	0.456	0.467	31.26	1.493	1.74
MSF3	.29.56	0.298	0.511	26,54	1.401	1.89
MSF4	33.45	0.356	0.501	25.46	1.401	1.73
MSF5	27.67	0.321	0.498	31.20	1.398	1.74
MSF6	29.54	0.397	0.403	26.50	1.399	1.83
MSF7	31.56	0.289	0.398	27.45	1.432	1.94
MSF8	31.48	0.357	0.423	25.67	1.471	1.83
MSF9	32.57	0.298	0.510	28.47	1.392	1.78
MSF10	31.89	0.321	0.397	32.45	1.405	1.92

Table 11 Post compressional parameters of the formulated Sucralfate tablets

Formulation Code	Average weight (mg)	Thickness (mm)	Hardness (KP)	% Friability	Disintegration Time (min)	% Drug Content
SF1	207.1±0.451	3.14±0.002	5.75±0.088	0.167	23.56±0.468	88.98
SF2	206.6±0.541	3.53±0.008	5.87±0.214	0.159	7.34±0.081	99.33
SF3	206.8±0.699	3.18±0.021	5.62±0.370	0.159	7.35±0.315	100.73
SF4	205.2±0.441	3.18±0.024	5.51±0.228	0.398	5.39±0.460	99.57
SF5	206.4±0.401	3.00±0.045	5.39±0.220	0.081	8.39±0.329	95.12
SF6	207.3±0.410	3.10±0.045	5.11±0.109	0.198	7.56±0.034	99.45
SF7	205.8±0.543	3.41±0.07	5.79±0.155	0.298	5.98±0.056	98.43
SF8	206.6±0.321	351±0.006	5.43±0.279	0.299	5.43±0.039	97.54
SF9	205.2±0.500	3.20±0.010	5.45±0.109	0.292	0.98±0.075	99.23
SF10	206.5±0.327	3.01±0.001	5.49±0.056	0.299	1.31±0.125	99.49

Table 12 Post compressional parameters of the formulated Metoprolol Succinate Tablets

Formulation Code	Average weight(mg)	Thickness (mm)	Hardness (KP)	% Friability	% Drug content	FLT (SEC)	TFT (HR)
MSF1	296.6±0.499	3.21±0.012	7.71±0.201	0.128	99.45	16	>22
MSF2	295.3±0.527	3.28±0.009	8.87±0.138	0.092	101.61	16	>20
MSF3	294.4±0.507	3.24±0.019	8.67±0.104	0.126	99.79	19	>21
MSF4	295.5±0.798	3.14±0.050	6.96±0.059	0.123	97.45	28	>18
MSF5	296.0.±0.470	3.92±0.068	7.45±0.121	0.154	99.34	19	>21
MSF6	295.9±0.392	3.15±0.034	9,34±0.151	0.165	100.01	32	>22
MSF7	296.2±0.506	2.45±0.009	9.34±0.106	0.125	99.81	31	>21
MSF8	295±0.512	2.98±0.065	9.23±0.034	0.127	98.43	29	>23
MSF9	296.1±0.554	2.56±0.050	8.91±0.069	0.129	98.74	34	>21
MSF10	295.8±0.431	3.52±0.005	7.98±0.004	0.179	99.59	12	>24

Table 13 Swelling index values observed from Metoprolol Succinate Tablets

TIME (HR)	% Swelling									
	MSF1	MSF2	MSF3	MSF4	MSF5	MSF6	MSF7	MSF8	MSF9	MSF10
0	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
1	79.34	98.12	83.5	82.7	79.7	76.4	71.1	67.5	65.4	72.9
2	81.76	100.82	99.26	98.26	91.0	89.1	99.54	85.4	81.5	98.54
3	93.8	115.5	101.6	122.54	105.5	105.1	149.2	99.54	102.6	126.12
4	105.5	123.8	125.7	143.56	115.7	125.1	153.5	105.7	118.5	151.45
5	125.5	164.4	142.3	174.5	143.5	134.2	164.5	137.9	134.7	182.45
6	164.8	171.4	173.3	185.7	145.6	187.6	184.2	167.6	172.1	200.52
7	188.4	182.5	185.0	201.6	199.4	201.4	191.4	187.5	199.5	220.61
8	190,8	199.3	199.5	207.2	201.5	210.5	211.2	211.4	201.5	238.91

Table 14 Accelerated Stability Study of Sucralfate Tablet

Tablets	After 7 days	After 15 days	After 30 days	Aftrer 45 Days	After 60Days	After 90Days
SF1	No Change	No Change	No Change	No Change	No Change	No change
SF2	No Change	No Change	No Change	No Change	No Change	slide black spots
SF3	No Change	No Change	No Change	No Change	No Change	No change
SF4	No Change	No Change	No Change	No Change	No Change	No Change
SF5	No Change	No Change	No Change	No Change	No Change	Black spot
SF6	No Change	No Change	No Change	No Change	No Change	No change
SF7	No Change	No Change	No Change	No Change	No Change	No change
SF8	No Change	No Change	No Change	No Change	No Change	No change
SF9	No Change	No Change	No Change	No Change	No Change	No change
SF10	No Change	No Change	No Change	No Change	No Change	No change

Table 15 Accelerated Stability Study of Metoprolol Succinate Tablet

Tablets	After 7 days	After 15 days	After 30 days	Aftrer 45 Days	After 60Days	After 90Days
MSF1	No Change	No Change	No Change	No Change	No Change	No change
MSF2	No Change	No Change	No Change	No Change	No Change	No change
MSF3	No Change	No Change	No Change	No Change	No Change	Slide yellowish
MSF4	No Change	No Change	No Change	No Change	No Change	No change
MSF5	No Change	No Change	No Change	No Change	No Change	Rare black spot
MSF6	No Change	No Change	No Change	No Change	No Change	Rare black spot
MSF7	No Change	No Change	No Change	No Change	No Change	No change
MSF8	No Change	No Change	No Change	No Change	No Change	No change
MSF9	No Change	No Change	No Change	No Change	No Change	No change
MSF10	No Change	No Change	No Change	No Change	No Change	No change

Table 16 Composition of Sucralfate layer (SF9) in SFMS tablets

SL.NO	INGREDIENTS OF BEST FORMULATION(SF9)	QUANTITY PER TABLET IN mg
1	Sucralfate	**100**
2	Sodium CMC	**12.5**
3	Calcium Phosphate	**1.3**
4	MCC	**1.5**
5	Sodium bicarbonate	**90**
6	Magnesium oxide	**85**
7	Aerosil/ colloidal SiO2	**2**
8	Hydroxy Propyl Methyl Cellulose	**5**
9	Sodiumlaurylsulfate	**2.5**
10	Alginic Acid	**0**
11	Magnesium Stearate	**0.2**
12	Sunset Yellow	**q.s**
13	SLS	**0**
	TOTAL	**300**

Table 17 Composition of Metoprolol Succinate (MSF2) layer in SFMS tablet

SL.NO	Ingredients best formulation (msf10)	Quantity per tablet in (mg)
1	Metoprolol Succinate	**50**
2	Ethyl cellulose	**50**
3	Xanthan Gum	**-**
4	Metoloze	**50**
5	Polyox	**-**
6	Eudragit	**-**
7	Methocel	**-**
8	Acrilic acid	**25**
9	Aerosil/ colloidal SiO2	**15**
10	Talc	**5**
11	Isopropyl alcohol (IPA)	**QS**
12	Purified water	**QS**
13	Sodium Bicarbonate	**5**
	TOTAL WEIGHT	**200**

Table 18 Post compressional parameters observed from the bilayered tablets of SFMS

SL. NO.	Parameter	Observed Value
1	Average Weight (mg)	500.7±0.866
2	Thickness (mm)	5.71±0.032
3	Hardness (KP)	7.2±0.312
4	% Friability	0.712
5	FLT (sec)	10
6	TFT (hr)	>24
7	DT(min)	2.04±0.157
8	Drug content (%)	99.98%

Table 19 Accelerated Stability Study of granules of Sucralfate(SF9) and Metoprolol Succinate (MSF10)of selected formulations

Granules	After 7 days	After 15 days	After 30 days	Aftrer 45 Days	After 60 Days	After 90 Days
SF9	No Change	No Change	No Change	No Change	No Change	No Change
MSF10	No Change	No Change	No Change	No Change	No Change	No Change

DT- Disintegration Time TFT-Total floating Time FLT- Floating lag Time

Table 20 Accelerated Stability Study and in vitro evaluation of Bi -layer Floating Tablet of Sucralfate and Metoprolol Succinate at different time period

Sl No	parameters	observed value	After 15 days	Aftrer 30 days	After 60 days	After 90 days
1	Average Weight(mg)	501.7±0.26	499.1±0.21	500.7±0.12	497.7±0.15	491.7±0.13
2	Thickness(mm)	5.99±0.111	5.98.±0.013	5.97.±0.021	5.99±0.115	5.98±0.215
3	Hardness (KP)	8.1±0.124	8.2±0.111	8.0±0.321	8.4±0.453	8.3±0.145
4	% Friability	0.599	0.657	0.768	0.923	0.884
5	DT	2.02±0.56	2.02±0.19	2.02±0.32	2.02±0.32	2.02±0.34
6	TFT(hr)	>22	>21	>22	>22	>24
7	FLT(SEC)	7.83	8.01	7.99	7.99	8.02
8	Drug Content in %	99.85	99.87	98.25	99.15	99.56

Table 21 Cumulative drug release of Sucralfate in 6.8 pH Phosphate buffer at 281nm

Concentration (µg/ml)	Absorbance at 281nm
0	0
5	0.3127±0.0002
10	0.2345±0.0001
15	0.7654±0.0003
20	0.8765±0.0001
25	0.9153±0.0004
R^2	0.987

Table 22 Cumulative drug release of Sucralfate Sucralfate in 0.1N HCl at 281nm

Concentration (µg/ml)	Absorbance at 281nm
0	0.0000
5	0.1111 ± 0.0003
10	0.2134 ± 0.0001
15	0.3127 ± 0.0001
20	0.7123 ± 0.0002
25	0.8951 ± 0.0004
R^2	0.912

Table 23 Cumulative drug release of Metoprolol Succinate in 0.1N HCl at 233nm

Concentration (µg/ml)	Absorbance at 281nm
0	0.0000
5	0.1679±0.0001
10	0.4356±0.0003
15	0.5432±0.0003
20	0.7123±0.0002
25	0.9152±0.0003
R^2	0.997

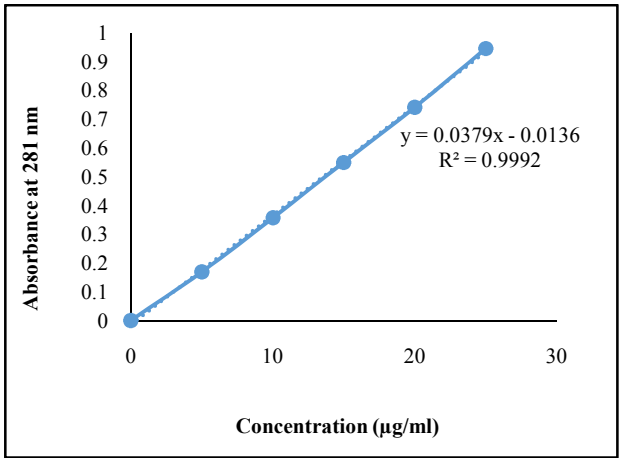

Fig 1 Calibration curve of Sucralfate in 6.8pH phosphate buffer at 281nm

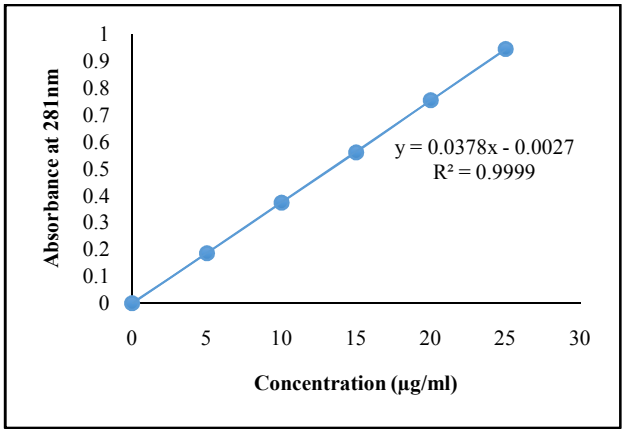

Fig 2 Cummulative drug release of Sucralfate in 0.1N HCl at 281nm

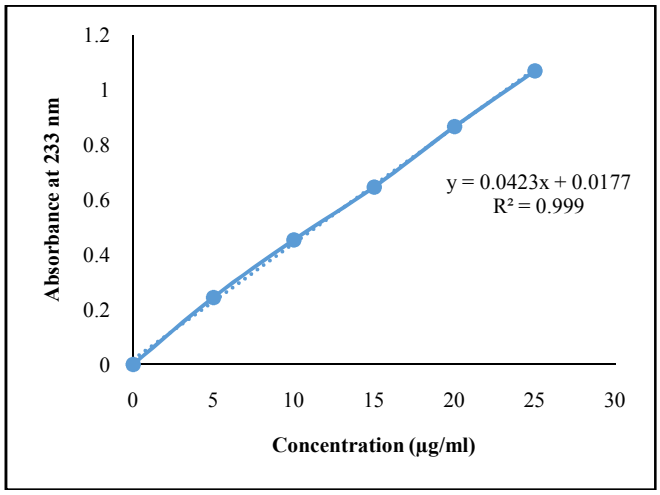

Fig 3 Cummulative drug release of Metoprolol Succinate in 6.8pH phosphate buffer at 233nm

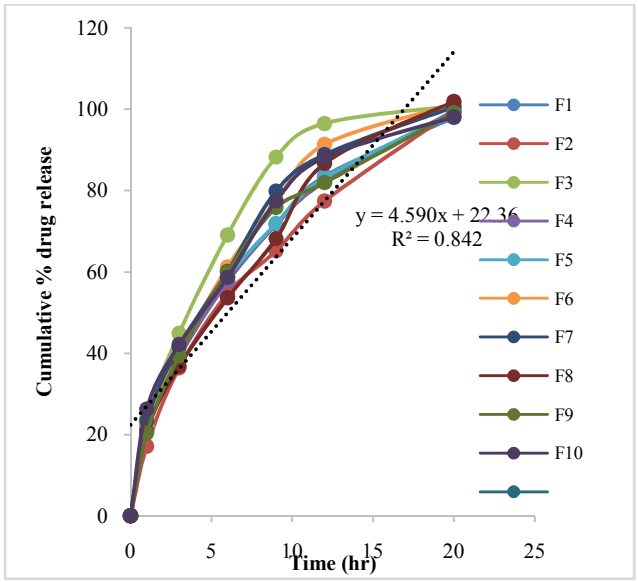

Fig 4 Zero order plots of Metoprolol Succinate formulations

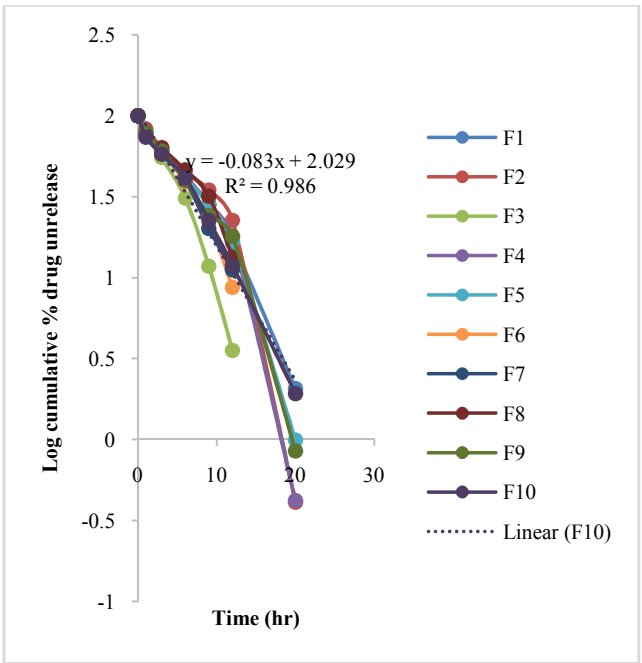

Fig 4 Zero order plots of Metoprolol Succinate formulations

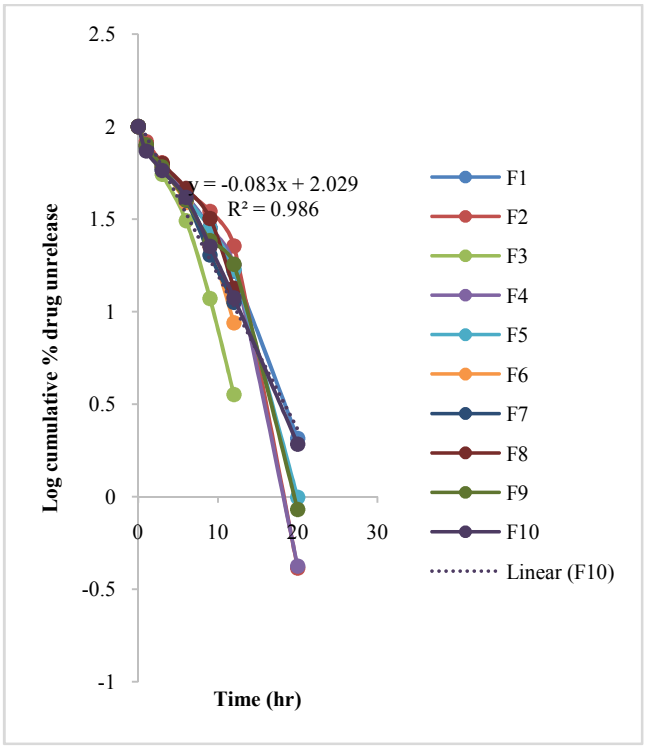

Fig 5 First order plots of Metoprolol Succinate formulations containing different polymer concentration

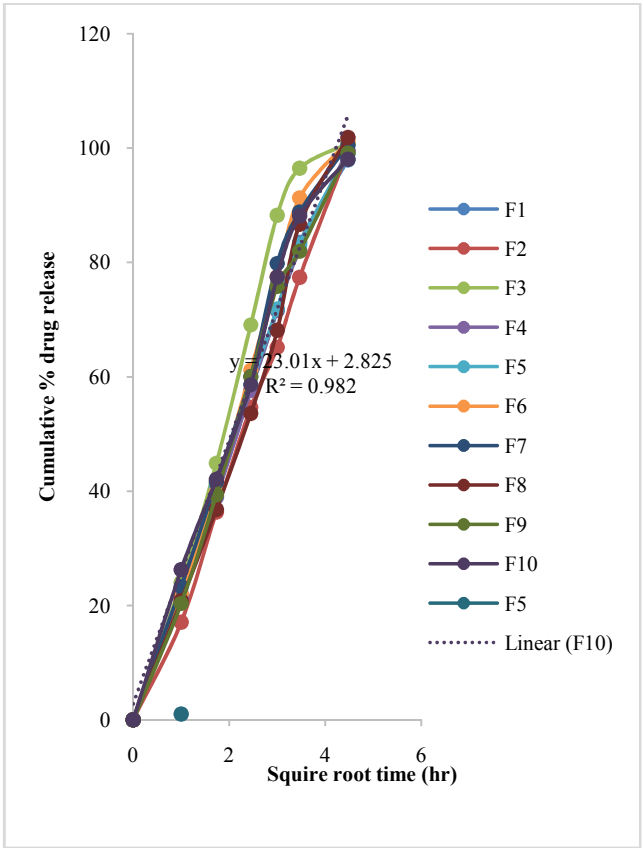

Fig 6 Higuchi plots of Metoprolol Succinate from formulations containing different polymers

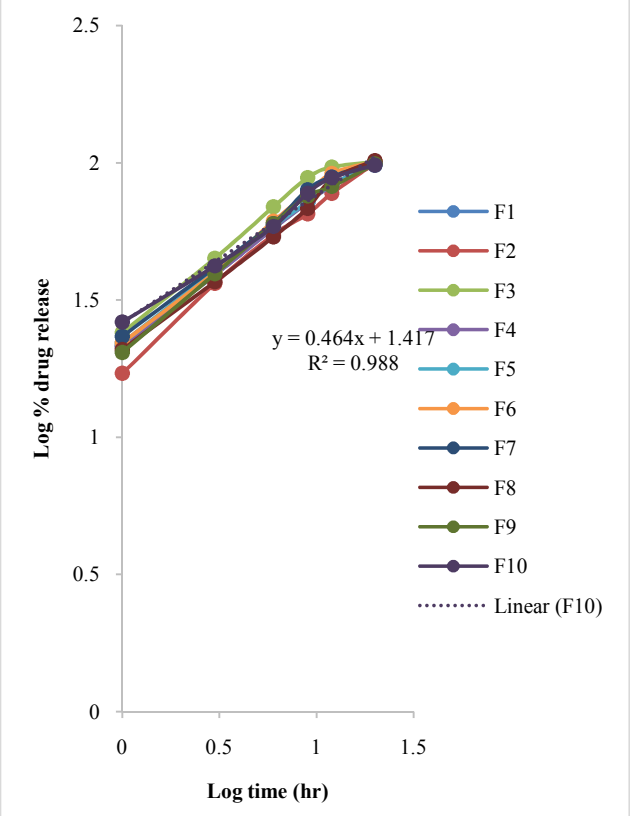

Fig 7 Pappas plots of Metoprolol Succinate from formulations containing different polymers

CONCLUSIONS

The result of present study indicate that after various types of in vitro evaluation and stability studies of 10 formulations of ulcer protective immediate release Sucralfate and 10 formulations of Antihypertensive Metoprolol Succinate as floating sustained release layer, the combination of formulations (SF9+MSF10) can fulfil all the criteria of IP standard and ICH guideline and provide the better composition of 150 mg oral controlled release tablet.(Bi Layered Floating Tablet). The present study can generate a new scope in optimization of formulations and clinical trials and can produce better identification in Gastro Retentive Drug Delivery System.

Acknowledgement

I would like to express my special thanks of gratitude to my Guide Dr Bibhuti Bhusan Panigrahi and Co Guide Dr Monoj Kumar Pani as well as The Principal who gave me a golden opportunity to proceed on my research work on the topic which helped in enhancement of my knowledge and ability.I am really thankful to them.

Secondly i would like to thank my parents, my family and supporting staffs who helped me a lot in fulfilment of the work.

Finally i would like to thank to God for blessing of further proceed.

Conflict of Intres

The authors declare that there no conflict of interest regarding the study.

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