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RESEARCH ARTICLE

PREPARATION AND IN VITRO EVALUATION OF OPTIMIZED FORMULATION OF BI- LAYERED FLOATING TABLET OF SUCRALFATE AND METOPROLOL SUCCINATE.

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Key words:-

Sucralfate, Metoprolol Succinate , Bi-layered Floating Tablet, GRDDS.

Abstract

Objective: The present study based upon the preparation and in vitro evaluation of optimized Bi layered floating tablet (OSFMS) having tablet weight of 400 mg.(214.88 mg of sucralfate & 186 mg of Metoprol succinate). **Method:** Selection of the formulation, pre compression study, preparation of tablet and in vitro evaluation of tablet. **Result:** In presence of Lactose MFL, MCC PH 101, Sodium Bicarbonate, Polysorbate 80, Cross povidone of majore amount in Sucralfate layer and in presence of HPMC K 100 M, Sodium Bicarbonate, Eudragit RSPO, Na CMC ,Sodium alginate, HPC, Ethyl Cellulose of majore amount in Metoprolol Succinate layer it produce (OSFMS) tablet having weight of 400 mg.(214.88 mg of Sucralfate & 186 mg of Metoprol succinate) produced average drug release 99.92 % and DT of Sucralfate was 1.04 min at acid medium of stomach and TFT of Metoprol Succinate at upper intesine was > 24hours. **Conclusion:** The optimized formulation of Sucralfate and Metoprolol Succinate (OSFMS) may be considered as a better formulation as Gastro Retaintive Drug Delivery System..

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Introduction:-

Bi-Layered tablet contain immediate and sustained release layer¹ The incorporated drug remain in gastric region for several hours and produce prolong gastric resistance time and improve bioavailability .It reduce drug waste and enhance the solubility of drug² . The drug release slowly at desired rate and increase GRT .and better control of fluctuations in plasma drug concentration³

Peptic Ulcer Disease [PUD] during pregnancy occurs due to imbalance between digestive juice in stomach and duodenum. It also occurs due to bacterial infections called Helico bacterial Pyrolli .(H.Pyrolli). PUD during pregnancy occurs heart burn,abdominalpain,weight loss, Black and deep coloured stool etc ⁴

Sucralfate (Sucrose Octasulphate + Aluminium Hydroxide) is an effective Antacid and H₂ receptor antagonist implemented for PUD. Sucrose octasulphate react with HCL produce viscous sticky substance that bind with ulcer site and adhere with ulcerated tissue. It protect ulcer against hydrogen ion back diffusion., pepsin, and bile and promote ulcer healing. Aluminium Hydroxide neutralise gastric acid⁵ It can be administrated in pregnancy and lactation⁶

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According to National High Blood Pressure Education Programme Working Group on High Blood Pressure⁷ Gestational Hypertension is referred as Pregnancy Induced Hypertension (PIH). It is a condition of High Blood Pressure during pregnancy. It leads to serious condition called Preeclampsia or Toxaemia after 20 weeks of pregnancy⁸

Metoprolol Succinate is a B-Blocker used to block the action⁹ of certain natural chemicals; Epinephrine that affect heart and blood vessel and lower heart rate. It is effective for treatment of blood pressure in pregnancy and lactation¹⁰. Having maintenance dose 100-200 mg daily in empty stomach with 200 ml of water¹¹

Both Sucralfate and Metoprolol succinate produce minor drug interaction in pregnancy and lactate mother¹²

The objective of present research based upon the preparation and in vitro evaluation of optimized Bi layered floating tablet (OSFMS) having tablet weight of 400 mg.(214.88 mg of sucralfate & 186 mg of Metoprolol succinate and to prove as a better formulation as Gastro Retentive Drug Delivery System..

MATERIALS AND METHODS:

2.1-Selection of formulation of Optimized Sucralfate and Metoprolol Succinate (OSFMS) Bi Layered Floating Tablet.

Table1:Composition of formulation of Optimized Sucralfate and Metoprolol Succinate (OSFMS) Bi Layered Floating Tablet

SL No	INGREDIENTS	Quantity per Ingredients in mg OSF (Optimized Sucralfate Layer)	INGREDIENTS	Quantity per Ingredients in mg OMSF (Optimized Metoprolol Succinate Layer)
1	SUCRALFATE	100	METOPROLOL SUCCINATE	50
2	CROSS POVIDONE	7	HPMC K 100 M	25
3	AEROSIL	1	SODIUM BICARBONATE	15
4	LACTOSE MFL	31.25	AEROSIL	3
5	MCC PH101	43.575	EUDRAGIT-RSPO	20
6	SODIUM BICARBONATE	15	EUDRAGIT-RLPO	7.5
7	POLYSORBATE 80	7	EUDRAGIT-RS100	5
8	HPC-L	5	Na CMC	17.5
9	MAGNESIUM STEARATE	3.75	SODIUM ALGINATE	15
10	SUNSET YELLOW (0.25%)	0.3125	HPC	12.5
11	PURIFIED WATER	qs	ETHYL CELLULOSE	10
	TOTAL WEIGHT	214	PVPK -90	2.5
12			TALC	3
13			IPA	Q.S
14			PURIFIED WATER	Q.S
15			TOTAL WEIGHT	186

2.2-Flow properties of lubricated granules.

The lubricated granules obtained from wet granulation of Sucralfate and Metoprolol Succinate with different excipients are evaluated for flow properties like bulk density, tapped density, compressibility index, Hausner's ratio and angle of repose

2.2.1-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.

$$\text{Bulk density, } \rho_B = \frac{W}{V_B} \quad \text{Tapped density, } \rho_T = \frac{W}{V_T}$$

2.2.2-Compressibility Index:

It was calculated by using the following formula

$$\text{Carr's Index or Compressibility Index (CI)} = 1 - \frac{\rho_B}{\rho_T} * 100$$

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

2.2.3-Hausner's Ratio: It is calculated by the following formula;

$$\text{Hausner's Ratio} = \frac{\rho_T}{\rho_B}$$

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

2.2.4 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;

$$\text{Angle of repose } (\theta) = \tan^{-1} (\text{height / radius}).$$

2.3- Accelerated stability study is done of lubricated granules.

Accelerated Stability study is done of 10 gm of each optimized batch. Accelerated stability study is done of lubricated granules of each formulations of Sucralfate and Metoprolol Succinate at at 45°C and 75% RH for a period of 3 months. The tablets were packed in 85mm HDPE bottles with an oxygen adsorbent, and a desiccant containing silica gel with cotton as filler. The granules were withdrawn after the regular interval of stability period, and evaluated for physical properties.

2.4-Flowproperties of lubricated granuls after 90 days of stability studies.

Comparison study is done between initial parameters of flow properties of granules and granules after 90 days of stability study of Sucralfate and Metoprolol Succinate

2.5--Preparation of Bi-layered tablets of OSFMS:

Following the optimized formulation Sucralfate layer and Metoprolol Succinate layer, Bilayered Floating tablets were prepared. The Bi-Layered tablets of Sucralfate and Metoprolol Succinate (OSFMS) 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,

2.6- The post compressial parameters ;

2.6.1-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.

$$\% \text{Weight variation} = \frac{\text{Average weight} - \text{individual weight}}{\text{individual weight}} \times 100$$

2.6.2-Thickness:

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

2.6.3-Hardness:

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

2.6.4-Friability:

Ten tablets were carefully dedusted prior to testing and weighed accurately (W_0). 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 (W_1). It is calculated from the following formula;

$$\% \text{ Friability} = 1 - \frac{W_1}{W_0} * 100$$

2.6.5-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.

2.6.6-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.

2.6.7-Total floating time (TFT):

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

2.6.8-Swelling index of Metoprolol Succinate tablets

The previously weighed (W_1) tablet was placed in USP apparatus type-I which was immersed in a bowel containing 900ml of 0.1N HCl and maintained at $37 \pm 0.2^\circ\text{C}$. 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 (Fig 6.7). The tablet was reweighed (W_2). The studies were repeated for all formulations in triplicate. The swelling index was calculated as follows:

$$\text{Swelling Index} = \frac{W_2 - W_1}{W_1} * 100$$

2.7-Determination of drug content of Sucralfate tablets:

Ten SF tablets were weighed accurately and then crushed well in a clean mortar and pestle. The powder equivalent to 25mg of the drug was weighed (W_s) and then transferred to a 100ml volumetric flask. 50ml methanol was added and sonicated for 5 minutes at 27°C . Then the volume was made up to 100ml using methanol (V_4). From this 4ml (V_5) was transferred to a 100ml volumetric flask and the volume was made up to 100ml (V_6) 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.

$$\% \text{ Drug Content} = \frac{AS}{AS} * \frac{W}{V_1} * \frac{V_2}{V_3} * \frac{V_4}{W_s} * \frac{V_6}{V_5} * \frac{AW}{L} * P$$

Where,

AS= Test absorbance

AS= Standard Absorbance

W= Weight of standard drug (25mg)

V_1 = Volume of solvent added to standard stock solution (100ml)

V_2, V_3 = 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%).

2.8-Determination of drug content of Metoprolol Succinate tablets: :

Ten MS tablets were weighed and crushed in a mortar with pestle. The crushed powder equivalent to 100mg of MS (W_s) 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 (V_4) using 0.1N HCl and agitated for 5 minutes. A portion of it was centrifuged at 3000rpm for 10 minutes. The centrifuged sample was filtered through 0.45 μm whatmann filter paper. 2 ml (V_5) of the filtered sample was pipetted out and transferred to a 100ml volumetric flask and the volume was made up to 100ml (V_6) with 0.1N HCl and the flask was shaken 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.

$$\% \text{ Drug Content} = \frac{AS}{AS} * \frac{W}{V_1} * \frac{V_2}{V_3} * \frac{V_4}{W_s} * \frac{V_6}{V_5} * \frac{AW}{L} * P$$

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%).

2.9- Release kinetic profile of Metoprolol Succinate:

Mechanism of drug release from MS tablets:

Different mathematical models were applied for describing the kinetics of the drug release process from the tablets.

The rate of drug release from tablets was determined by finding the best fit of the dissolution data to distinct models:

zero order (eq. 1), first order (eq. 2), and mechanism of drug release from Higuchi (eq. 3)

$Q_t = k_0 t$ ----- (eq. 1) $Q_t = Q_\infty (1 - e^{-k_1 t})$ ----- (eq. 2)

$Q_t = k_H t^{1/2}$ ----- (eq. 3)

Where, Q_∞ being the total amount of drug in the matrix, k_0 the zero order kinetic constant, k_1 the first order kinetic constant and k_H representing the Higuchi rate constant. The best fit model was found by using correlation coefficient values (R), using MS EXCEL.

The data obtained from in vitro dissolution studies were fitted to zero-order, first-order, and Higuchi equations. The dissolution data obtained were plotted as Time versus cumulative percent drug released as zero order, Time versus cumulative percent drug remaining as First order release kinetics, Square root of time versus cumulative percent drug released as Higuchi equation

Result and discussion:-

3.1- Flow properties of lubricated granules of Sucralfate and Metoprolol Succinate. Optimized formulations.

Table-2:

Formulation Code	Angle of Repose (Θ)	Bulk Density (g/ml)	Tapped Density (g/ml)	Compressibility Index (%)	Hausner's Ratio	%LOD
OSF	20.16	0.215	0.498	27.12	1.342	1.82
OMS	21.24	0.218	0.523	32.57	1.457	1.94

OSF- Optimized Sucralfate layer.OSFMS- Optimized Metoprolol succinate layer.

3.2-Accelerated stability study of lubricated granules of Sucralfate and Metoprolol Succinate Optimized formulations

It shows there is no any physical or chemical changes observed after 90 days at proper temperature and relative humidity condition.

Table-2:

GRANULES	AFTER 7 DAYS	AFTER 15 DAYS	AFTER 30 DAYS	AFTER 45 DAYS	AFTER 60 DAYS	AFTER 90 DAYS
OSF	No Change	No Change	No Change	No Change	No Change	NO change
OMS	No Change	No Change	No Change	No Change	No Change	NO change

OSF- Optimized Sucralfate layer.OMS- Optimized Metoprolol succinate layer.

3.3- Flow properties of lubricated granules of Sucralfate and Metoprolol Succinate Optimized formulations after 90 days of stability studies produce following result.

Table-3:

Formulation Code	Angle of Repose (Θ)	Bulk Density (g/ml)	Tapped Density (g/ml)	Compressibility Index (%)	Hausner's Ratio	%LOD
OSF	21.71	0.219	0.501	25.10	1.234	1.79
OMS	22.34	0.210	0.524	31.67	1.405	1.67

OSF- Optimized Sucralfate layer. OMS- Optimized Metoprolol Succinate layer.

3.4- Post compressional parameters OSFMS Bi layered Floating Tablet.

Table 4:

SL. NO.	Parameter	Bilayered Floating Tablets of OSFMS observed values
1	Average Weight (mg)	400±0.379
2	Thickness (mm)	5.21±0.125
3	Hardness (KP)	8.1±0.291
4	% Friability	0.543
5	DT of Sucralfate layer in minute	1.04±0.154
6	FLT of Metoprolol Succinate layer in seconds	6.45
7	TFT of Metoprolol Succinate Layer in hrs	>24

3.5 : Release kinetic profile of Sucralfate

The cumulative drug release study of Sucralfate in 0.1 N HCl from OSFMS at 281 nm produce averagely 99.78 % drug release.

3.6 : Release kinetic profile of Metoprolol Succinate:

The cumulative drug release study of Metoprol succinate in 0.1 N HCl at 233 nm produce produce averagely 100.06% drug release release within 20 hours.

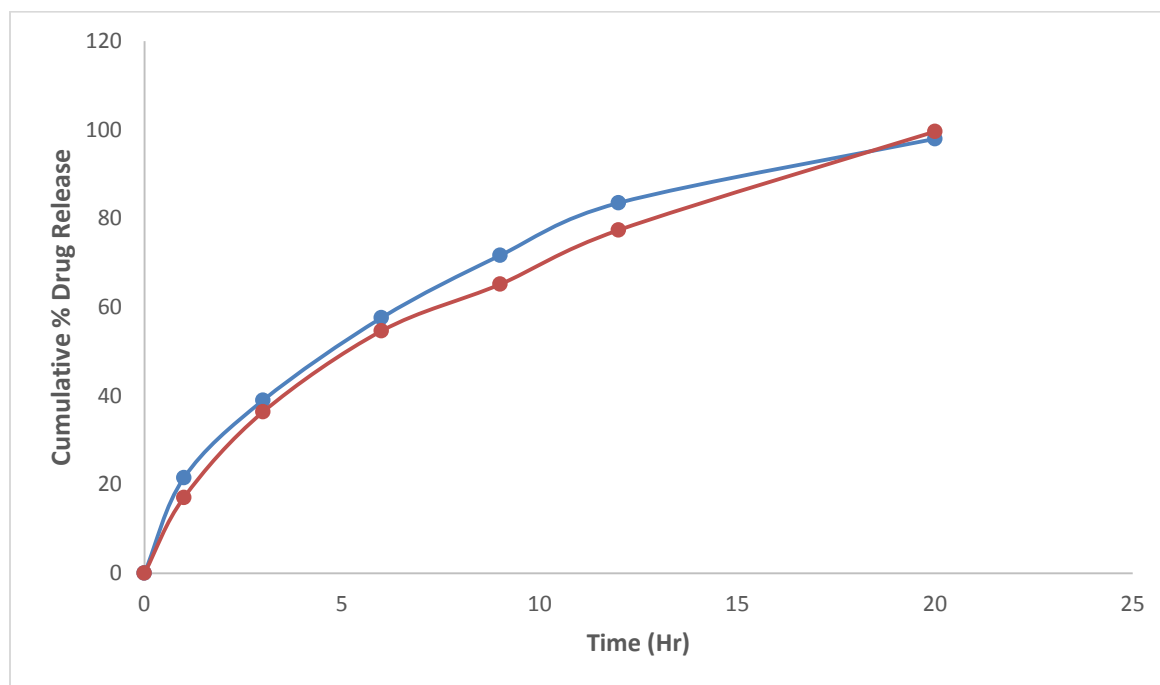


Figure-1: Cumulative drug release study of Sucralfate and Metoprolol Succinate in 0.1 N HCl from OSFMS.

3.7-Avrage drug release of OSFMS in % ($99.78 + 100.06 = 199.84/2 = 99.92$)

3.8- Accelerated stability study of Sucralfate and Metoprolol Succinate Optimized Tablets After 90 days of Accelerated stability study at proper temperature and humidity condition produce near about similar physical parameters which shows better stability of formulation.

Table-5:

GRANULES	AFTER 7 DAYS	AFTER 15 DAYS	AFTER 30 DAYS	AFTER 45 DAYS	AFTER 60 DAYS	AFTER 90 DAYS
OSF	No Change	No Change	No Change	No Change	No Change	NO change

OMS	No Change	No Change	No Change	No Change	No Change	NO change
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Conclusion:-

After in vitro evaluation and stability studies of **optimized Bi layered floating tablet (OSFMS) having tablet weight of 400 mg.(214.88 mg of sucralfate & 186 mg of Metoprol succinate)**. can fulfil all the criteria of IP standard and ICH guideline. Sucralfate in acidic medium produce averagely 99.78 % drug release. Within 20 hours Metoprolol Succinate produce averagely 100.06% drug release in acidic medium and identified as better formulation for further studies. 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.

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Conflict of intrest:-

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