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RESEARCH ARTICLE

DEVELOPMENT AND OPTIMIZATION OF BI LAYERED FLOATING TABLET OF SUCRALFATE AND METOPROLOL SUCCINATE.

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Abstract

Objective: To optimize and develop Bi layered floating tablet (SFMS) containing ulcer protective Sucralfate as immediate release layer and anti hypertensive Metoprolol Succinate as sustained release layer.

Method: 15 formulations of Sucralfate and 10 formulations of Metoprolol Succinate is taken. By changing the concentration of Superdisintegrant, Surfactants, Alkalizing agents & Binding agents of Sucralfate and changing concentrations of Alkalizing agents and Polymers of Metoprolol Succinate the OSFMS (**Optimized Sucralfate and Metoprolol Succinate Formulation**) is generated.. Result: Within 5 minutes in acidic medium, 7% Superdisintegrant (Crosspovidone), 7% Surfactant (Polysorbate-80), 15% Alkalizing agents (Sodium bicarbonate), 5% HPC (Binding agent) averagely produce 68.56% drug release. Within 20 hours in acidic medium, 30% Alkalizing agents (Sodium bicarbonate), 50% Soluble polymer (HPMC K), 40% Polymer (Udrigid RSPO, 35% HPC Polymer (NaCMC), 30% Polymer (Sodium alginate), 25% Polymer (HPC), 20% Polymer, Udrigid RS), 5% HPC Polymer (PVPK) produce averagely 100.06% drug release. Conclusion: The optimized formulation 400 mg tablet weight of OSFMS (Optimized Sucralfate and Metoprolol Succinate Formulation) produce better result and identified as better formulation for further studies.

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Introduction:-

The term Optimization¹ is defined as to make perfect, effective, or functional as possible. It is the process of finding the best way of using the existing resources while taking into the account of all factors that influences decision in any experiments. The Modern Pharmaceutical optimization involves systematic Design of Experiment (DOE) to improve formulation irregularities.

Bilayer floating drug delivery system is combined principle of Bi-Layered Tablet as well as floating mechanism.² Drug absorption from G.I.T depends upon contact time with intestinal mucosa.³ Bi-layered Tablet materials involve both the compressibility and consolidation.⁴ Bi-Layered tablet contain immediate and sustained release layer.⁵ 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 drug.⁶ The drug release slowly at desired rate and increase GRT and better control of fluctuations in plasma drug concentration.⁷

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Both Sucralfate and Metoprolol succinate produce minor drug interaction in pregnancy and lactate mother⁸ Both the drugs are administrated in empty stomach in presence of acid medium⁹. They act at stomach as well as at upper part of small intestine and produce better bioavailability¹⁰

The present study is to develop and to optimize¹¹ Bi-Layered Floating Tablet of Sucralfate and Metoprol succinate to formulate a new formulation producing better release at low dose. and to make a comparison study between the initial formulation and optimized formulation.

Materials and methods:-

15 formulations of Sucralfate and 10 formulations of Metoprol Succinate are taken..¹²

Table 1:-List of excipients used for the preparation of Sucralfate layer (SF1---SF9)

INGREDIENTS		QUANTITY PER TABLET IN MG								
		SF 1	SF 2	SF 3	SF 4	SF 5	SF 6	SF 7	SF 8	SF 9
1	Sucralfate	100	100	100	100	100	100	100	100	100
2	Crospovidone	0	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25
3	Calcium carbonate	23	25	25	25	0	25	0	0	0
4	Aerosil	1	1	1	1	1	1	1	1	1
5	Lactose MHF	31.25	31.25	31.25	31.25	31.25	31.25	31.25	31.25	31.25
6	MCC PH 101	48.45	45.2	44.575	44.575	74.575	49.575	49.575	49.825	46.075
7	Magnesium Stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
8	Sodium bicarbonate	5	5	5	5	0	0	25	25	25
9	Polysorbate 80	0	0	0	0.625	0.625	0.625	0.625	0.375	0.375
10	SLS	0	0	0.625	0	0	0	0	0	0
11	Sunset yellow	0.312	0.3125	0.3125	0.3125	0.3125	0.3125	0.3125	0.3125	0.3125
12	Purified Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
	Tablet wt in (mg)		214.5	214.5	214.5	214.5	214.5	214.5	214.5	214.5

Table 2:-List of excipients used for the preparation of Sucralfate layer (SF10---SF15)

Sl	INGREDIENTS	QUANTITY PER TABLET IN MG					
No		SF 10	SF 11	SF12	SF 13	SF 14	SF 15
1	Sucralfate	100	100	100	100	100	100
2	Crospovidone	6.25	6.25	3.75	8.75	6.25	6.25
3	Aerosil	1	1	1	1	1	1
4	Lactose MFL	31.25	31.25	31.25	31.25	31.25	31.25
5	MCC PH101	48.575	43.575	48.575	43.575	52.325	39.825
6	Magnesium Stearate	0.5	0.5	0.5	0.5	0.5	0.5
7	Sodium Bicarbonate	25	25	25	25	18.75	31.25
8	Polysorbate 80	0.375	0.375	0.375	0.375	0.375	0.375
9	HPC-L	1.25	6.25	3.75	3.75	3.75	3.75
10	Sunset Yellow	0.3125	0.3125	0.3125	0.3125	0.3125	0.3125
11	Purified Water	q.s	q.s	q.s	q.s	q.s	q.s
	Total Weight	214.5	214.5	214.5	214.5	214.5	214.5

Table 3:-List of excipients used for the preparation of Metoprolol Succinate sustained release layer .

SL. NO	INGREDIENTS	QUANTITY PER TABLET IN MG									
		MSF 1	MSF 2	MSF 3	MSF 4	MSF 5	MSF 6	MSF 7	MSF 8	MSF 9	MSF10
1	Metoprolol Succinate	50	50	50	50	50	50	50	50	50	50
2	HPMC K 100M	100	100	100	100	100	100	100	100	100	75
3	SODIUM BICARBONATE	75	100	100	100	100	100	100	100	100	100
4	AEROSIL	3	3	3	3	3	3	3	3	3	3
6	EUDRAGIT RSPO	30	30	-	-	-	-	-	-	-	30
7	EUDRAGIT RLPO	-	-	30	-	-	-	-	-	-	-
8	EUDRAGIT RS100	-	-	-	30	-	-	-	-	-	-
8	Na CMC	-	-	-	-	30	-	-	-	-	-
9	SODIUM ALGINATE	-	-	-	-	-	30	-	-	-	-
10	HPC KLUCEL HF	-	-	-	-	-	-	30	-	-	-
11	PVPK 90	-	-	-	-	-	-	-	30	-	-
12	ETHYL CELLULOSE	-	-	-	-	-	-	-	-	30	-
13	TALC	3	3	3	3	3	3	3	3	3	3
14	IPA	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
15	PURIFIED WATER	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

Optimization of Sucralfate formulation.**In vitro drug release study of Sucralfate tablets by changing concentration of different formulations.**

These in-vitro drug release studies of Sucralfate tablets were carried out as per USP guidelines. The dissolution method and equipment were validated before the study. The dissolution of all batches of tablets was carried out using LABINDIA DISSO 2000 with automatic sampler, a USP Apparatus-II Paddle type apparatus with 0.1N HCl (and 6.8pH phosphate buffer respectively) as dissolution media with volume of 900ml. The dissolution medium was subjected to degassing by placing the dissolution vessel with medium in a water bath at $37 \pm 2^{\circ}\text{C}$. The paddle speed was set at 75rpm and the temperature was maintained at $37 \pm 0.5^{\circ}\text{C}$. The sampling volume was 10ml with a rinsing volume of 3ml and with 10ml replacing volume. The sampling intervals were 5, 10, 15, 20, 30 and 45minutes. The collected samples were analyzed as pooled samples at 281nm using UV-Spectrophotometer

In-vitro drug dissolution data of Sucralfate Tablet with or without (**Super disintegrants - Crosspovidone**) in presence of 0.1 HCL and 6.8 Phosphate buffer are studied. [SF1 (Nill),SF2 (1%),SF9(3%),SF12(5%),SF13(7%)]

Table 4:-Cumulative drug dissolution data of Sucralfate Tablets formulated with and without (Superdisintegrant - Crosspovidone) [SF1 (Nill),SF2 (1%)]

Time (min)	Cumulative % drug release			
	0.1N HCL		6.8 pH phosphate buffer	
	SF1(Nill)	SF2(1%)	SF1(Nill)	SF2(1%)
0	0	0	0.000	0.000
5	3.974	26.169	4.891	53.011

10	5.976	43.395	10.796	71.969
15	13.964	77.174	26.306	83.625
20	32.618	79.845	56.797	100.289
30	48.731	81.843	70.387	-
45	50.824	95.191	75.755	-
R	0.9489	0.9706	0.9608	0.9963
k (min ⁻¹)	0.017	0.0664	0.0333	0.3022
T ₅₀ (min)	40.7	10.4	20.7	2.3
T ₉₀ (min)	135.2	34.7	68.8	7.6

Table 5:-Cumulative drug dissolution data observed from Sucralfate Tablets formulated with different concentrations of (Superdisintegrant - Croscopovidone) present in the concerned formulation.[SF9(3%),SF12(5%),SF13(7%)]

Nil – Without Superdisintegrants. % - Quantity of Superdisintegrant

Time (min)	Cumulative % drug release					
	0.1N HCL			6.8pH phosphate buffer		
	SF9(3%)	SF12(5%)	SF13(7%)	SF9(3%)	SF12(5%)	SF13(7%)
0	0	0	0.00	0	0	0
5	56.98	63.689	91.42	74.3	40.9	80.1
10	81.83	70.08	90.05	99.4	90.2	101.7
15	89.08	86.864	95.50	100.5	95.7	-
20	94.03	91.045	102.14	-	97.9	-
30	98.37	101.602	-	-	101	-
45	101.41	98.727	-	-	-	-
R	0.9965	0.9826	0.9951	0.9482	0.9874	0.999
k (min ⁻¹)	0.1954	0.1813	0.2822	0.428	0.2088	0.6032
T ₅₀	4.3	3.8	2.5	1.6	3.3	1.1
T ₉₀	14.4	12.7	8.2	5.4	11	3.8

SF1: Without Superdisintegrant; SF2: With super disintegrant(1%)

Fig 1:-In vitro drug dissolution profiles of Sucralfate Tablets formulated with and without different (Superdisintegrant - Croscopovidone) at 0.1N HCL and 6.8 pH respectively.

SF9: 3% super disintegrant; SF12: 5% superdisintegrant; SF13: 7% superdisintegrant

Fig 2:-In vitro drug dissolution profiles of Sucralfate tablets formulated with different concentrations of (Superdisintegrant - Crosspovidone) at 0.1N HCL and 6.8 pH respectively.

Drug dissolution data of with different (Surfactants ;SLS and Polysobate -80)in presence of 0.1 HCL & 6.8 Phosphate buffer is done' [SF2(Nill),SF3(SLS),SF4(P-80 0.7%), SF7(P-80 0.5%) ,SF8 (P-80 0.3%)]

Table 6:-Cumulative drug dissolution data of Sucralfate Tablets formulated with different (Surfactants :SLS and Polysorbate-80) [SF2(Nill),SF3(SLS),SF4(P-80 0.7%),]

Time (min)	Cumulative % drug release					
	0.1N HCL			6.8pH phosphate buffer		
	SF2 (Nill)	SF3 (5%SLS)	SF4 (7%P_80)	SF2 (Nill)	SF3 (5%SLS)	SF4 (0.7% P-80)
0	0	0	0	0.000	0.00	0.00
5	26.169	5.721	96.74	53.011	3.68	55.64
10	43.395	36.026	77.33	71.969	25.24	81.80
15	77.174	47.145	93.94	83.625	54.53	99.53
20	79.845	58.776	101.55	100.289	63.62	101.08
30	81.843	71.529	-	-	86.22	-
45	95.191	79.309	-	-	97.93	-
R	0.9706	0.9827	0.9813	0.9963	0.9783	0.9261
k (min ⁻¹)	0.0664	0.0397	0.2723	0.3022	0.0705	0.2501
T50	10.4	18.3	2.5	2.3	9.8	2.8
T90	34.7	16.8	8.5	7.6	37.7	9.2

Table7:-Cumulative drug dissolution data of Sucralfate Tablets formulated with different concentrations of (Surfactants :SLS and Polysorbate-80) [SF7(P-80 0.5%) ,SF8 (P-80 0.3%)]

Time (min)	Cumulative % drug release			
	0.1N HCL		6.8pH phosphate buffer	
	SF7 (5%P-80)	SF8 (3%P-80)	SF7 (5%P-80)	SF8 (3%P-80)

0	0	0	0	0
5	64	48.99	58.4	55.5
10	71.7	75.18	95.1	78.4
15	82.8	84.62	100.6	93.5
20	86.9	88.41	-	99.3
30	100.6	100.35	-	100.1
45	-	-	-	-
R	0.9639	0.9868	0.9706	0.935
k (min ⁻¹)	0.1744	0.173	0.3801	0.2173
T ₅₀ (min)	4	4	1.8	3.2
T ₉₀ (min)	13.2	13.3	6.1	10.6

Nil – Without Surfactants. % - Quantity of Surfactants present in the concerned formulation.

SF2: Without surfactant; SF3: With SLS; SF4: With polysorbate80 (0.7%)

Fig 3:-In vitro drug dissolution profiles of Sucralfate tablets formulated with different (Surfactants :SLS and

Polysorbate-80) at 0.1N HCL and 6.8 pH respectively

SF7: 0.5% polysorbate80 ; SF8: 0.3% Polysorbate80

Fig 4:-In vitro drug dissolution profiles of Sucralfate tablets formulated with different (Surfactants :SLS and Polysorbate-80) at 0.1N HCL and 6.8 pH respectively.

Drug dissolution data of with different (Alkalizing agents ; CaCO_3 and NaHCO_3) in presence of 0.1 HCL & 6.8 Phosphate buffer is done [SF4-(Nil),SF5-30% CaCO_3 ,SF6-25% ; CaCO_3 , SF7-20% CaCO_3 ,SF9,-20% NaHCO_3 , SF14-15% NaHCO_3 SF15-25% NaHCO_3]

Table 8:-Cumulative drug dissolution data of Sucralfate Tablets formulated with and without (Alkalizing agents : CaCO_3 and NaHCO_3) [SF4-(Nil),SF5-30% CaCO_3]

Time (min)	Cumulative % drug release			
	0.1N HCL		6.8 pH phosphate buffer	
	SF4 (Nil)	SF5 30% CaCO_3	SF4 (Nil)	SF5 30% CaCO_3
0	0	0	0.00	0
5	66.74	11.43	55.64	3.5
10	77.33	17.89	81.80	34.3
15	93.94	24.03	99.53	71.6
20	101.55	38.16	101.08	86.2
30	-	49.82	-	100.1
45	-	56.36	-	-
R	0.9813	0.983	0.9261	0.9529
k (min ⁻¹)	0.2723	0.0201	0.2501	0.1583
T ₅₀ (min)	2.5	34.5	2.8	9.1
T ₉₀ (min)	8.5	114.6	9.2	29.6

Table 9:-Cumulative drug dissolution data of Sucralfate Tablets formulated with different (Alkalizing agents: CaCO_3 and NaHCO_3) [SF6-25% ; CaCO_3 , SF7-20% CaCO_3]

Time (min)	Cumulative % drug release			
	0.1N HCL		6.8pH phosphate buffer	
	SF6 25% CaCO_3	SF7 20% CaCO_3	SF6 25% CaCO_3	SF7 20% CaCO_3
0	0	0	0.00	0
5	53.98	64	68.00	58.4
10	76.25	71.7	92.30	95.1

15	82.37	82.8	95.20	100.6
20	84.67	86.9	100.70	-
30	100.06	100.6	-	-
45	-	-	-	-
R	0.9589	0.9639	0.9858	0.9706
k (min ⁻¹)	0.1491	0.1744	0.2755	0.3801
T ₅₀ (min)	4.7	4	2.5	1.8
T ₉₀ (min)	15.4	13.2	8.4	6.1

Nil – Without Alkalizing agents.% - Quantity of Alkalizing agents present in the concerned formulation

Table 10:-Cumulative drug dissolution data of Sucralfate Tablets formulated with different concentrations of (Alkalizing agent : CaCO₃ and NaHCO₃) [SF9,-20% NaHCO₃ , SF14-15% NaHCO₃ SF15-25% NaHCO₃]

Time (min)	Cumulative % drug release					
	0.1N HCL			6.8pH phosphate buffer		
	SF9 30% NaHco3.	SF14 25% NaHco3	SF15 25% NaHco3	SF9 30% NaHco3	SF14 25% NaHco3	SF15 25% NaHco3
0	0	0	0	0	0	0
5	56.98	38.629	97.583	74.3	57.7	60.9
10	81.83	69.34	89.838	99.4	74.1	101.1
15	89.08	78.61	92.229	100.5	100.7	-
20	94.03	84.494	100.826	-	101.9	-
30	98.37	96.051	-	-	-	-
45	101.41	98.683	-	-	-	-
R	0.9965	0.997	0.9715	0.9482	0.9886	0.9999
k (min ⁻¹)	0.1954	0.0997	0.279	0.428	0.2935	0.6292
T50	4.3	7	2.5	1.6	2.4	1.1
T90	14.4	23.1	8.3	5.4	7.8	3.7

SF4: Without alkalizing agent; SF5: Alkalizing agent (30%)

Fig 5:-In vitro drug dissolution profiles of sucralfate tablets formulated with and without (Alkalizing agent CaCO_3 and NaHCO_3) at 0.1N HCL and 6.8 pH respectively

SF6: Calcium carbonate 25% ; SF7: Sodium bicarbonate 20%

Fig 6:-In vitro drug dissolution profiles of sucralfate tablets formulated with different (Alkalizing agents CaCO_3 and NaHCO_3) at 0.1N HCL and 6.8 pH respectively.

SF9: 20% alkalizing agent; SF14: 15% alkalizing agent; SF15: 25% alkalizing agent

Fig 7:-In vitro drug dissolution profiles of Sucrafate tablets formulated with different concentrations of (Alkalizing agent CaCO_3 and NaHCO_3) at 0.1N HCL and 6.8 pH respectively

2.2.5- Drug dissolution data with (Binding agents HPC) in presence of 0.1 HCL & 6.8 Phosphate buffer of [SF8-(Nil), SF9(2%), SF9--(3%) , SF10- (1%), SF11 (5%)]

Table 11:-Cumulative drug dissolution data of Sucralfate tablets formulated with and without (Binding agent:HPC) of [SF8-(Nil), SF9(2%), SF9--(3%)]

Time (min)	Cumulative % drug release			
	0.1N HCL		6.8pH phosphate buffer	
	SF8(Nil)	SF9(2%)	SF8(Nil)	SF9(2%)
0	0	0	0	0
5	48.99	56.98	55.5	74.3
10	75.18	81.83	78.4	99.4
15	84.62	89.08	93.5	100.5
20	88.41	94.03	99.3	-
30	100.35	98.37	100.1	-
45	-	101.41	-	-
R	0.9868	0.9965	0.935	0.9482
k (min-1)	0.173	0.1954	0.2173	0.428
T50	4	4.3	3.2	1.6
T90	13.3	14.4	10.6	5.4

Table12:-Cumulative drug dissolution data of Sucralfate Tablets formulated with different concentrations of (Binding agents:HPC) [SF9--(3%) ,SF10- (1%), SF11 (5%)]

Nil – Without Binding agents.

% - Quantity of Binding agents present in the concerned formulation.

Time (min)	Cumulative % drug release					
	0.1N HCL			6.8pH phosphate buffer		
	SF9(3%)	SF10(1%)	SF11(5%)	SF9(3%)	SF10(1%)	SF11(5%)
0	0	0	0	0	0	0
5	56.98	95.53	53.74	74.3	69.4	65.4
10	81.83	90.22	78.49	99.4	100.2	83.6
15	89.08	92.4	88.44	-	-	84.2

				100.5		
20	94.03	98.62	89.3	-	-	93.9
30	98.37	101.98	99.74	-	-	100.7
45	101.41	-	100.68	-	-	-
R	0.9965	0.9829	0.9507	0.9482	0.999	0.9701
k (min ⁻¹)	0.1954	0.2155	0.1541	0.428	0.5773	0.1831
T50	4.3	3.2	4.5	1.6	1.2	3.8
T90	14.4	10.7	14.9	5.4	4	12.6

SF8: Without binder; SF9: With binder(2%)

Fig 8:-In vitro drug dissolution profiles of sucralfate tablets formulated with and without (Binding agents :HPC) at 0.1N HCL and 6.8 pH respectively.

SF9: 3% binder; SF10: 1% binder; SF11: 5% binder

Fig 9:-In vitro drug dissolution profiles of sucralfate tablets formulated with different concentrations of (Binding agents:HPC) at 0.1N HCL and 6.8 pH respectively.

Optimization of Metoprolol succinate formulation.**In vitro drug release studies of Metoprolol Succinate tablets:**

In vitro drug release studies were performed for all the formulated NA tablets. The method and equipment used for the study were previously validated. The tablets were placed in sinkers and were dropped into 6 bowls of dissolution apparatus (USP Type-II) . Previously degassed 900ml of 0.1N HCl was employed as dissolution media. The paddle speed was set at 100rpm and temperature was maintained at $37 \pm 0.5^\circ\text{C}$. The sampling volume was 10ml and the same was replenished with fresh dissolution medium. The samples were collected at 1, 3, 6, 9, 12 and 20 hours. The samples were collected as pooled samples and were analyzed at 233 nm using UV-Spectrometer.

Cumulative % drug release data were prepared of Metoprolol Succinate observed from formulations containing different concentrations of (Alkalizing agents;Sodium Bicarbonate). [MSF1(11%),MSF2 (13%)]

Table 13:-

Time (hr)	Cumulative % drug release in 0.1 N HCl	
	MSF1(11%)	MSF2(30%)
0	0.00	0.00
1	21.53	17.08
3	38.99	36.37
6	57.61	54.65
9	71.67	65.16
12	83.51	77.39
20	97.94	99.59
R	0.9844	0.9600
k (hr ⁻¹)	0.1418	0.1181
T ₅₀ (hr)	4.88	5.86
T ₉₀ (hr)	16.23	19.49
Best fit model	Peppas	Higuchi
n value	0.5194	0.5845

MSF1-(11% Sodium Bicarbonate), MSF2-(13% Sodium Bicarbonate),

Fig 10:-Drug release profiles of Metoprolol Succinate from tablets containing different concentrations of (Alkalizing agents;Sodium Bicarbonate).

2.3.3.-Cumulative % drug release data prepared of Metoprolol Succinate from formulations containing different concentrations of (HPMC K) [MSF2(33%) ,MSF10 (23%).]

Table 14:-

Time (hr)	Cumulative % drug release in 0.1 N HCl	
	MSF2(50%)	MSF10 (23%)
0	0.00	0.00
1	17.08	26.27
3	36.37	42.10
6	54.65	58.61
9	65.16	77.47
12	77.39	88.14
20	99.59	98.08
R	0.9600	0.9931
k (hr ⁻¹)	0.1181	0.1661
T ₅₀ (hr)	5.86	4.17
T ₉₀ (hr)	19.49	13.86
Best fit model	Higuchi	Peppas
n value	0.5845	0.5

Fig 11:-Effect of HPMC concentration on cumulative drug release profile of Metoprol Succinate MSF2-(33% HPMC), MSF10-(23% HPMC)

Cumulative % drug release data of Metoprolol Succinate observed from tablets formulated with different polymers. [MSF2(Eudragit RSPO-40%),MSF3(Sodium CMC -35%) ,MSF4(Sodium Alginate-30%),MSF5 (HPC-25%),MSF6 (EC-20%),MSF7(Eudragit- LPO-15%),MSF8 (Eudragit-RS100-10%),MSF9(EC-10%)]

Table 15:-

E-RSPO =Eudragit –RSPO , E-LPO = Eudragit LPO ,EC-Ethyl Cellulose

Time (hr)	Cumulative % drug release in 0.1 N HCl

	MSF2 E-RSPO 40%	MSF3 NaCMC 35%	MSF4 NaAlginate 30%	MSF5 HPC 25%	MSF6 EC 20%	MSF7 E-LPO 15%	MSF8 E-RS 100 10%	MSF9 EC 10%
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	17.08	24.03	21.39	22.04	22.09	23.31	20.84	20.36
3	36.37	44.87	39.02	40.56	39.95	41.59	36.80	39.38
6	54.65	69.07	57.65	58.66	61.18	60.06	53.61	59.98
9	65.16	88.24	71.61	71.88	77.48	79.83	68.14	75.82
12	77.39	96.45	82.18	83.11	91.32	88.81	86.65	81.97
20	99.59	100.73	99.58	99.01	101.16	100.52	101.87	99.15
R	0.9600	0.9910	0.94	0.9663	0.9892	0.99	0.9697	0.965
k (hr ⁻¹)	0.1181	0.2785	0.1349	0.139	0.1995	0.1749	0.1618	0.135
T ₅₀ (hr)	5.86	2.48	5.13	4.98	3.47	3.96	4.28	5.13
T ₉₀ (hr)	19.49	8.26	17.06	16.55	11.54	13.16	14.23	17.04
Best fit model	Higuchi	Peppas	Peppas	Peppas	Peppas	Peppas	Peppas	Higuchi
n value	0.5845	0.5103	0.5228	0.5098	0.5331	0.5094	0.5448	0.5400

Fig12:-Cumulative % drug release profiles of Metoprolol Succinate observed from formulations containing different polymers:[MSF2(EudragitRSPO-40%),MSF3(SodiumCMC-35%),MSF4(SodiumAlginate-30%),MSF5 (HPC-25%),MSF6(EC-20%),MSF7(Eudragit-LPO-15%),MSF8(Eudragit-RS100-10%),MSF9(EC-10%)]

Fig13:-First order plots of Metoprolol Succinate from formulations containing different polymers: [MSF2(Eudragit RSPO-40%),MSF3(Sodium CMC -35%) ,MSF4(Sodium Alginate-30%),MSF5 (HPC-25%),MSF6 (EC-20%),MSF7(Eudragit- LPO-15%),MSF8 (Eudragit-RS100-10%),MSF9(EC-10%)]

2.4- Consideration of Optimized formulation: Table-16,Table-17, Table-18

Optimized formulations are developed by comparing the cumulative drug release of Sucralfate and Metoprolol Succinate at different time periods.

RESULT AND DISCUSSION:-

1. **3.1-Cummulative drug dissolution data of Sucralfate formulation.**
2. **3.1.1-** Cummulative drug dissolution data of Sucralfate formulation shows 71.42% release at 5th minute in acid medium (0.1HCL) in presence of 7% (Crosspovidone as Superdisintegrant). **Table-4,Table-5,Fig-1,Fig-2 .**
3. **3.1.2-** Cummulative drug dissolution data of Sucralfate formulation shows 66.74 %release at 5th minute in acid medium (0.1 HCL) in presence of 7% (Polysorbate-80 as Surfactant) **Table-6,Table7,Fig-3,Fig-4**
4. **3.1.3-** Cummulative drug dissolution data of Sucralfate formulation shows 70.583% release at 5th minute in acid medium(0.1 HCL) in presence of 15% Sodium Bicarbonate as Alkalizing agent. . **Table-8,Table-9,Table-10, Fig-5,Fig-6,Fig-7 .**
5. **3.1.4-** Cummulative drug dissolution data of Sucralfate formulation shows 65.53% release at 5th minute in acid medium(0.1 HCL) in presence of 5% Hydroxy Propyl Cellulose as binding agent. . **Table-11, Table-12, Fig-8,Fig-9.**
6. **3.2-Cummulative drug dissolution data of Metoprol Succinate formulation.**
7. **3.2.1-** Cummulative drug dissolution data of Metoprol Succinate formulation shows 99.59 % release at 20th minute in acid medium (0.1 HCL) in presence of 30% of Sodium Bicarbonate as Alkalizing agent. **Table-13, Fig-10**
8. **3.2.2-** Cummulative drug dissolution data of Metoprol Succinate formulation shows 99.46 % release at 20th minute in acid medium (0.1 HCL) in presence of 50% of HPMC as soluble polymer. **Table-14,Fig-11**
9. **3.2.3-** Cummulative drug dissolution data of Metoprol Succinate formulation shows release at 20th minute in acid medium (0.1 HCL) in presence of different polymers ; 99.39% at 40% of Udragit- RSPO ,100.73 % at 35% of CMC, 99.58% at 30% of Sodium alginate ,99.01% at 25% HPC ,101.16 % at 20% Ethyl Cellulose ,100.52 % at 15 % Udragit RLPO ,101.87 % at 10% Eudragit RS ,99.15% at 5% Ethyl Cellulose. **Table-15,Fig-13**
10. **3.3-Result of optimization of Sucralfate layer. Table-16**
11. Within 5 minutes in 0.1 HCL medium , 7% Superdisintegrant (Crosspovidone) produce 71.42 % drug release in SF13, 7% Surfactant (Polysorbate-80) produce 66.74 % drug release in SF4 ,15% Alkalizing agents(Sodium bicarbonate) produce 70.583% drug release in SF15, 5% HPC (Binding agent) produce 65.53%drug release in SF10.

Table 16:-Result of optimization of Sucralfate layer.

SI NO	INGREDIENTS	MEDIUM	%OF INGRADIENTS TAKEN	TIME IN MINUTES	% OF DRUG RELEASE	FORMULATION

1	Superdisintegrant (Croscopollose)	0.1 HCL	7%	5 th	71.42 %	SF13
2	Surfactant (Polysorbate-80)	0.1 HCL	7%	5 th	66.74%	SF4
3	Alkalizing agents(Sodium bicarbonate)	0.1 HCL	15%	5 th	70.583%	SF15
4	HPC (Binding agent)	0.1 HCL	5%	5 th	65.53%	SF10

3.4-Result of optimization of Metoprol Succinate layer. Table-17

Within 20 minutes in 0.1 HCL medium , 30% Alkalizing agents(Sodium bicarbonate) produce 99.59 % drug release in MSF2, 50% Solublepolymer (HPMC K) produce 99.46 % drug release in MSF2 ,40% Polymer (Udragid RSPO) produce 99.59% drug release in MSF2, 35% HPC Polymer(NaCMC) produce 100.73% drug release in MSF3,30% Polymer (Sodiumalginate) produce 99.58% drug release in MSF4, 25% Polymer (HPC) produce 99.01 % drug release in MSF5 , 20% Polymer (Udragid RS) produce 101.87% drug release in MSF8, 5% HPC Polymer (PVPK) produce 99.15% drug release in MSF9.

Table-17:-Result of optimization of Metoprolol Succinate layer.

SI NO	INGREDIENTS	MEDIUM	% OF INGREDIENTS TAKEN	TIME IN MINUTES	% OF DRUG RELEASE	FORMULATION
1	Alkalizing agent (Sodium bicarbonate)	0.1 HCL	30%	20 th	99.59 %	MSF2
2	Solublepolymer (HPMC K)	0.1 HCL	50%	20 th	99.46%	MSF2
3	Polymer (Udragid RSPO)	0.1 HCL	40%	20 th	99.59%	MSF2
4	Polymer(NaCMC)	0.1 HCL	35%	20 th	100.73%	MSF3
5	Polymer (Sodiumalginate)	0.1HCL	30%	20th	99.58%	MSF4
6	Polymer(HPC)	0.1 HCL	25%	20th	99.01%	MSF5
7	Polymer (EC)	0.1 HCL	20%	20th	101.16%	MSF6
8	Polymer (Udragid RLPO)	0.1 HCL	15%	20th	100.52%	MSF7
9	Polymer (Udragid –RS)	0.1 HCL	10%	20th	101.87%	MSF8
10	Polymer(PVPK)	0.1 HCL	5%	20th	99.15%	MSF9

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

Table 18:-

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	LACTOSEMFL	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

Conclusion:-

The optimized formulation 400 mg tablet weight of OSFMS (Optimized Sucralfate and Metoprolol Succinate Formulation) Sucralfate in acidic medium produce averagely 68.56% drug release within 5 minutes. Within 20 hours Metoprolol Succinate produce averagely 100.06% drug release release in acidic medium and identified as better formulation for further studies.

Future aspects:

The development and optimization of Bi-Layered Floating Tablet of Sucralfate and Metoprol Succinate produce a new era to formulate a new formulation producing better release at low tablet weight can full fill the proper therapeutic effect of the drugs and it generate a new scope for future generations.

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Conflict of interest:

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

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