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# OPTIMIZATION OF BI LAYERED FLOATING TABLET OF SUCRALFATE AND METOPROLOL SUCCINATE

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## ABSTRACT

**Objective:** To optimize 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 Superdisintigrant, Surfectants, 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% Superdisintigant (Crosspovidone), 7% Surfectant (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% Soluablepolymer (HPMC K), 40% Polymer (Udragid RSPO, 35% HPC Polymer(NaCMC), 30% Polymer (Sodiumalginate), 25% Polymer (HPC), 20% Polymer, Udragid 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.

**KEYWORDS:** Optimization. Sucralfate, Metoprolol Succinate, Bi-layered Floating Tablet.

## 1-INTRODUCTION

The term Optimization[1] 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 Morden

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]

Both Sucralfate and Metoprolol succinate produce minor drug interaction in pregnancy and lactate mother.[8] Both the drugs are administrated in empty stomach in presence of acid medium.[9] They act at stomach as well as at upper part of small intestine and produce better bioavilability.[10]

The present study is to develop and to optimize.[11] 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.

## 2- MATERIALS AND METHODS

**2.1-** 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 No | INGREDIENTS | QUANTITY PER TABLET IN MG | | | | | |
|---|---|---|---|---|---|---|---|
| | | 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 | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | MSF1 | MSF2 | MSF3 | MSF4 | MSF5 | MSF6 | MSF7 | MSF8 | MSF9 | 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 |

**2.2- Optimization of Sucralfate formulation**

**2.2.1**- 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 $37\pm2^0$C. The paddle speed was set at 75rpm and the temperature was maintained at $37\pm0.5^0$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.

**2.2.2-**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%)].

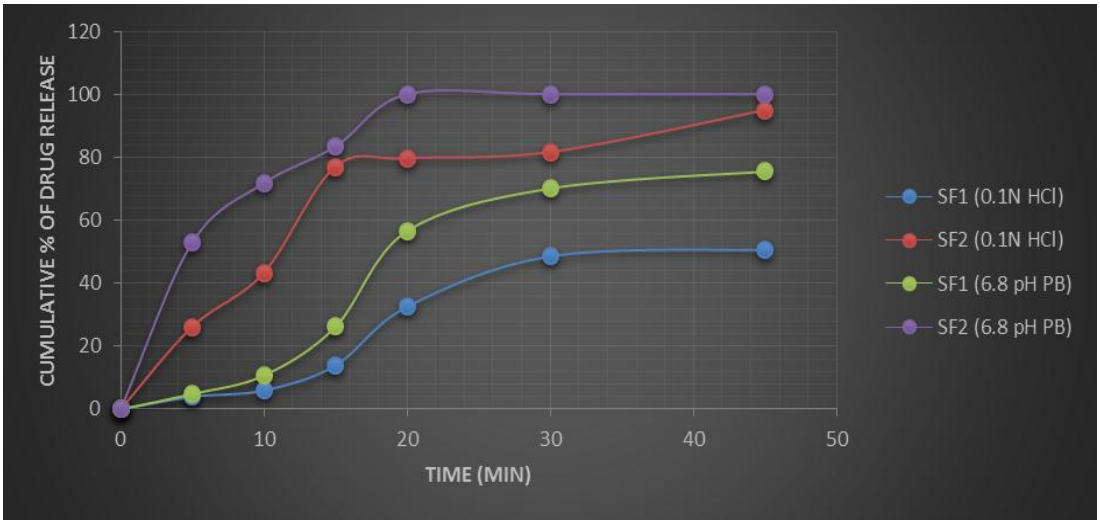
**Table 4: Cumulative drug dissolution data of Sucralfate Tablets formulated with and without (Superdisintegrant - Crosspovidone) [SF1 (Nill), SF2 (1%)].**

| 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 - Crosspovidone) present in the concerned formulation. [SF9(3%), SF12(5%), SF13(7%)].**
Nill – Without Superdisintigrants. % - Quantity of Superdisintigrant

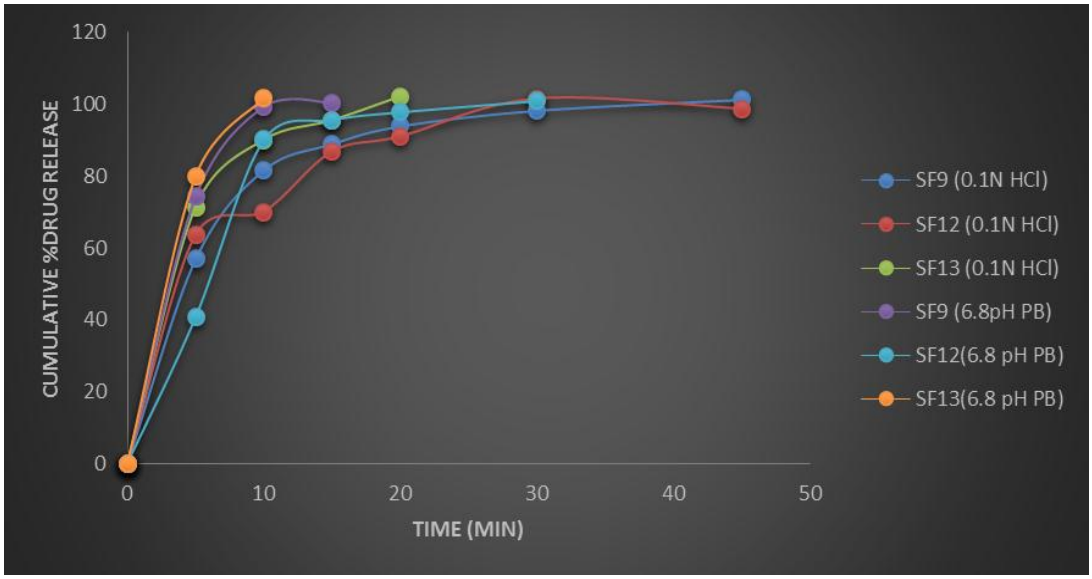
| Time (min) | Cumulative % drug release | | | | | |
|---|---|---|---|---|---|---|
| | 0.1N HCL | | | 6.8pH phosphate buffer | | |
| | SF9(3%) | SF12(5%) | SF13(7%) | SF9(3%) | SF12(5%) | SF13(7%) |
| 0 | 0 | 0 | 0.00 | 0 | 0 | 0 |
| 5 | 56.98 | 63.689 | 91.42 | 74.3 | 40.9 | 80.1 |
| 10 | 81.83 | 70.08 | 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 |
| T50 | 4.3 | 3.8 | 2.5 | 1.6 | 3.3 | 1.1 |
| T90 | 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 - Crosspovidone) 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.**

**2.2.3.**-Drug dissolution data of with different (**Surfectants; 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%)].

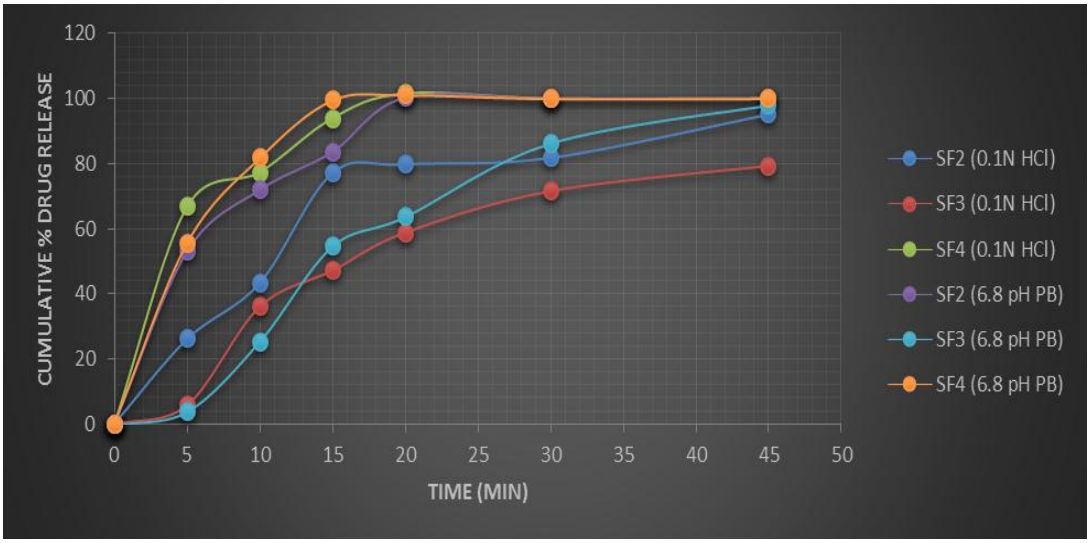
**Table 6: Cumulative drug dissolution data of Sucralfate Tablets formulated with different (Surfactants: SLS and Polysorbate-80) [SF2(Nill), SF3(SLS), SF4(P-80 0.7%),].**

| 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 |

**Table 7: 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%)].**

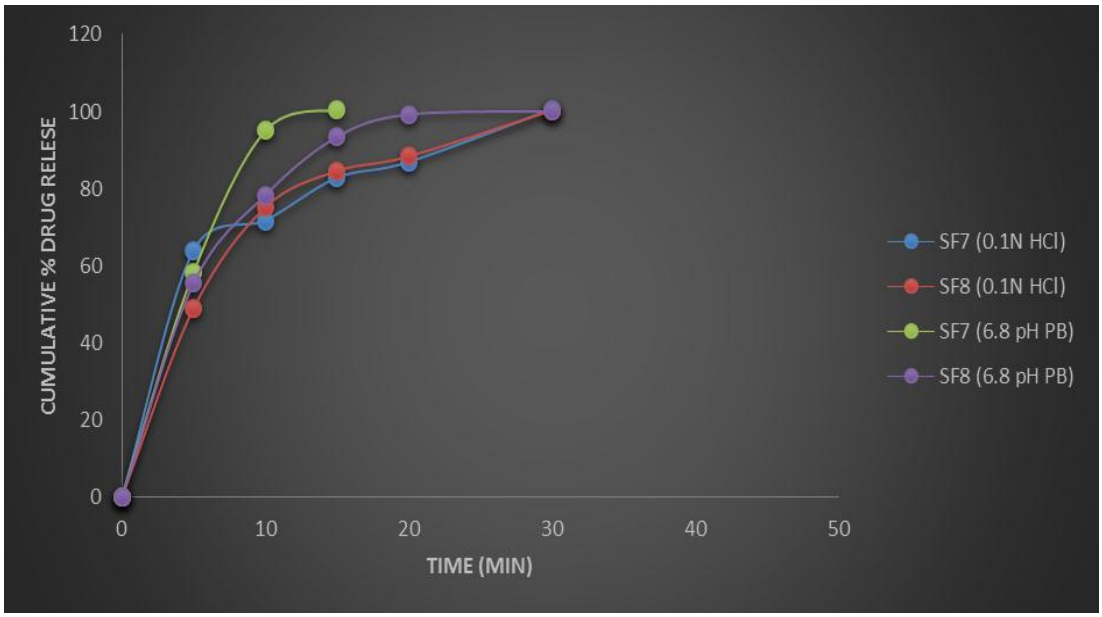
| Time (min) | Cumulative % drug release | | | |
|---|---|---|---|---|
| | 0.1N HCL | | 6.8pH phosphate buffer | |
| | SF7 (5%P-80) | SF8 (3%P-80) | SF7 (5%P-80) | SF8 (3%P-80) |
| 0 | 0 | 0 | 0 | 0 |
| 5 | 64 | 48.99 | 58.4 | 55.5 |
| 10 | 71.7 | 75.18 | 95.1 | 78.4 |
| 15 | 82.8 | 84.62 | 100.6 | 93.5 |
| 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 |

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




SF2: Without surfactant; SF3: With SLS; SF4: With polysorbate 80 (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% poysorbate 80; SF8: 0.3% Polysorbate 80.

**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.**

**2.2.4**-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-(Nill), 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: $CaCo_{3\ and,\ NaHco3.}$) [SF4-(Nill), SF5-30%$CaCo_{3]}$.**

| Time (min) | Cumulative % drug release | | | |
|---|---|---|---|---|
| | 0.1N HCL | | 6.8 pH phosphate buffer | |
| | SF4 (Nill) | SF5 30% $CaCo_3$ | SF4 (Nill) | 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 |

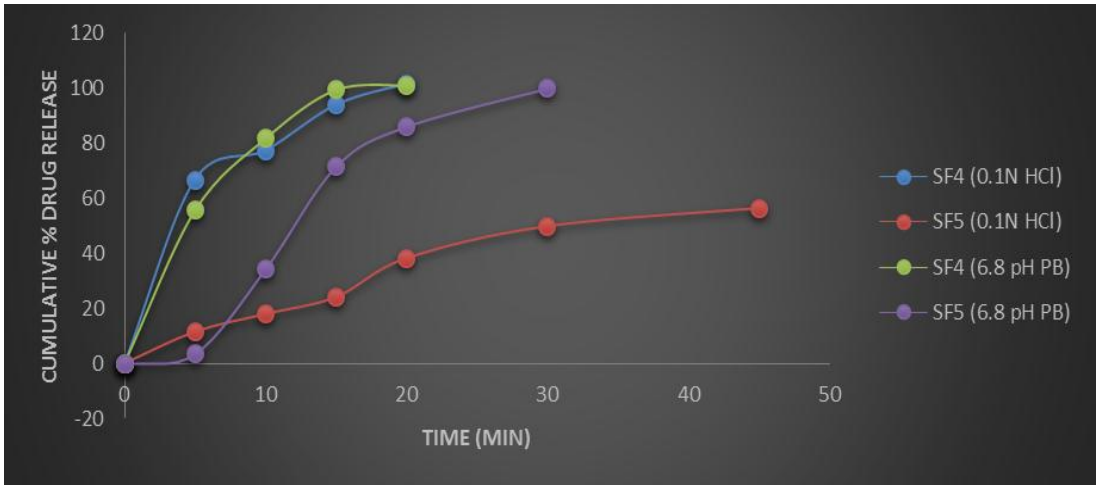
**Table 9: Cumulative drug dissolution data of Sucralfate Tablets formulated with different (Alkalizing agents: $CaCo_{3\ and,\ NaHco3.}$) [SF6-25%; $CaCO_3$, SF7-20%$CaCO_3$].**

| 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 |

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

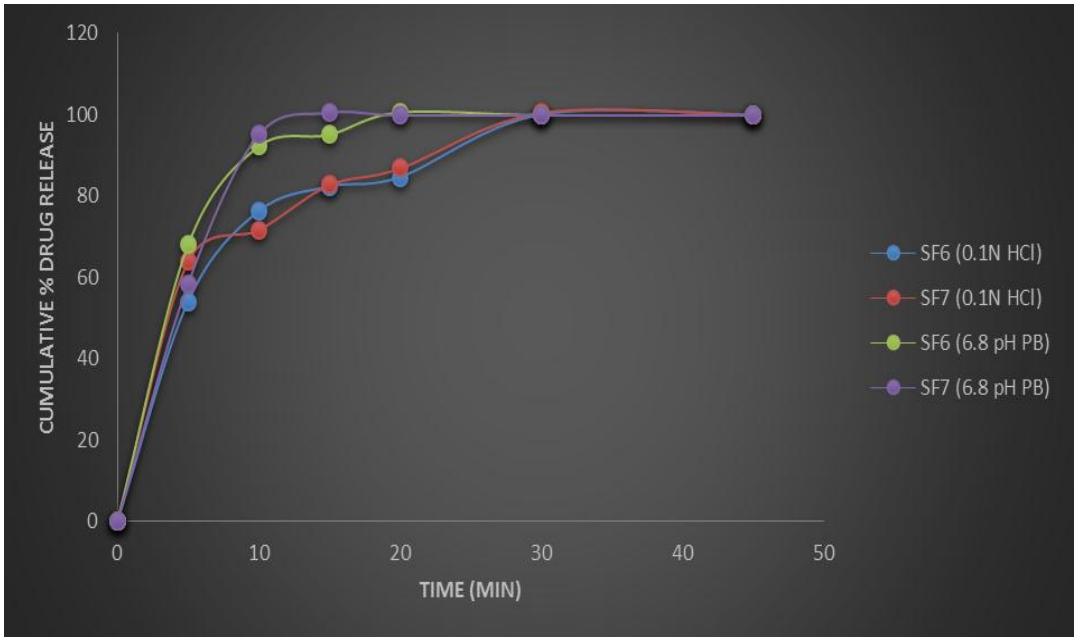
**Table 10: Cumulative drug dissolution data of Sucralfate Tablets formulated with different concentrations of (Alkalizing agent: $CaCo_{3\ and}$ $NaHCO_{3)}$ [SF9,-20% $NaHCO_3$, SF14-15% $NaHCO_3$ SF15-25% $NaHCO_3$].**

| 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 |



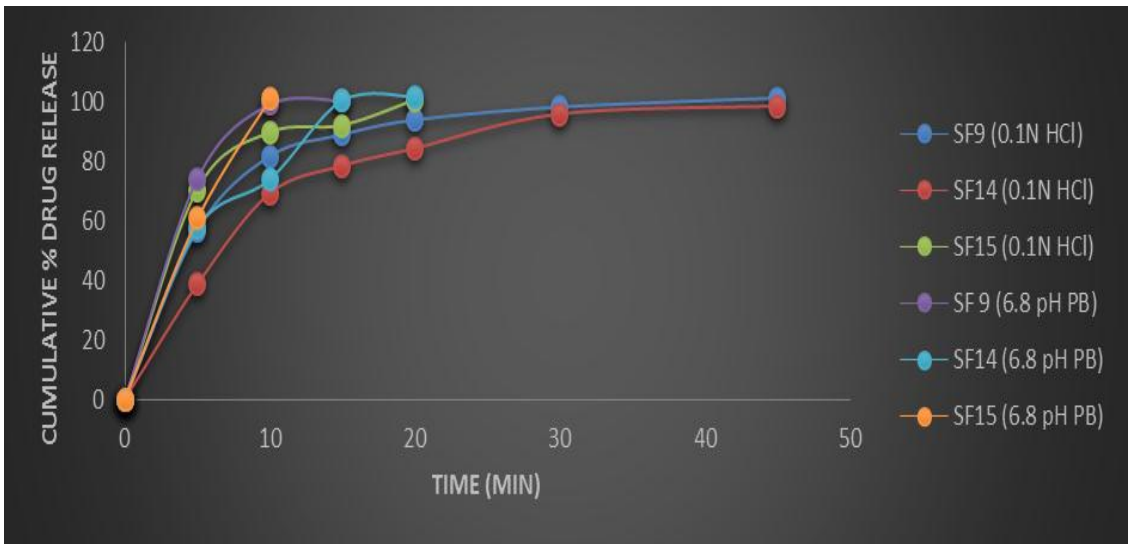

SF4: Without alkalizing agent; SF5: Alkalizing agent (30%).

**Fig 5: In vitro drug dissolution profiles of sucralfate tablets formulated with and without (Alkalizing agen $CaCo_{3\ and}$ $NaHCO_{3}$)t 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-(Nill), 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-(Nill), SF9(2%), SF9--(3%)].**

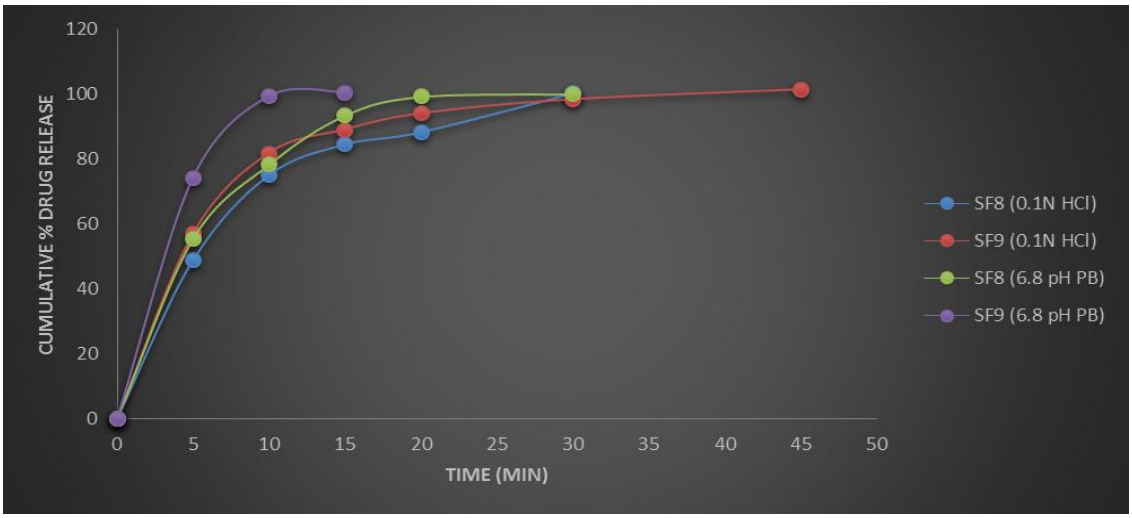
| Time (min) | Cumulative % drug release | | | |
|---|---|---|---|---|
| | 0.1N HCL | | 6.8pH phosphate buffer | |
| | SF8(Nill) | SF9(2%) | SF8(Nill) | SF9(2%) |
| 0 | 0 | 0 | 0 | 0 |
| 5 | 48.99 | 56.98 | 55.5 | 74.3 |
| 10 | 75.18 | 81.83 | 78.4 | 99.4 |
| 15 | 84.62 | 89.08 | 93.5 | 100.5 |
| 20 | 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 |

**Table 12: Cumulative drug dissolution data of Sucralfate Tablets formulated with different concentrations of (Binding agents: HPC) [SF9--(3%), SF10- (1%), SF11 (5%)]**

Nill – Without Binding agents.

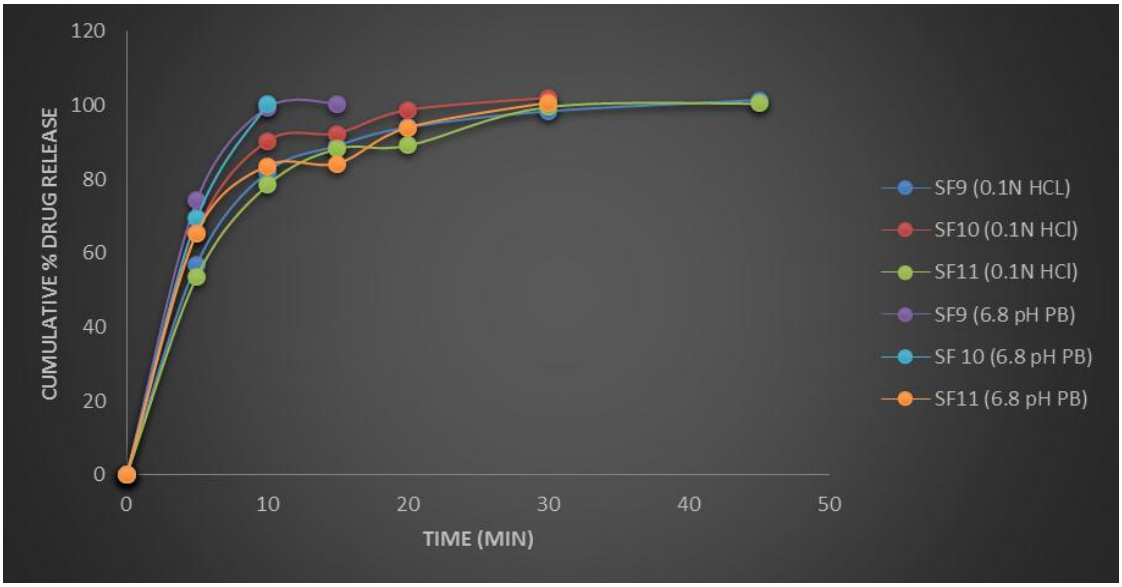
% - Quantity of Binding agents present in the concerned formulation.

| 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 | 100.5 | - | 84.2 |
| 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.**

### 2.3- Optimization of Metoprolol succinate formulation

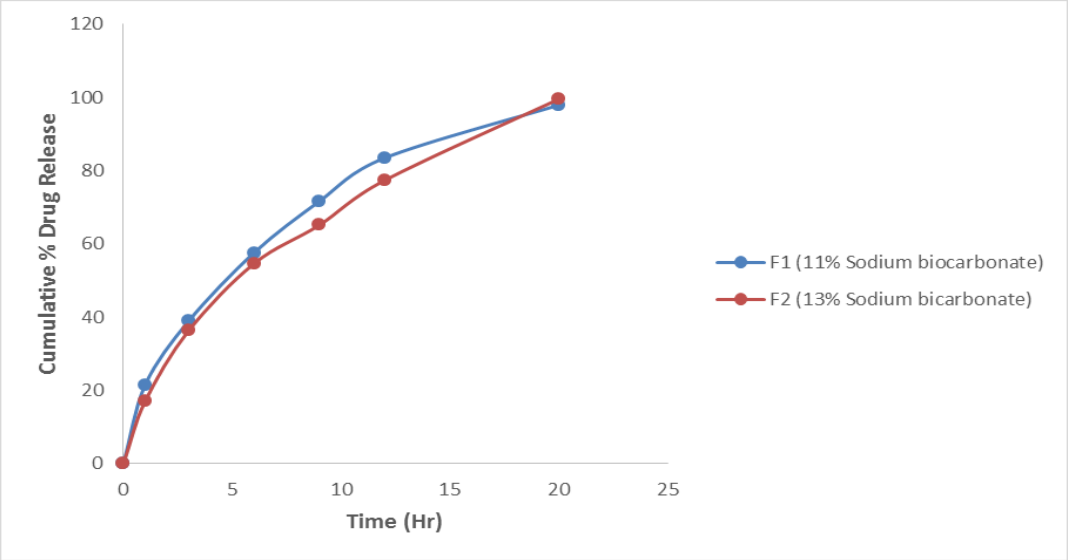
**2.3.1-In vitro drug release studies of Metoprolol Succinate tablets:** In vitro drug release studies were performed for all the formulated NA tablets. The method and equipment used for the study were previously validated. The tablets were placed in sinkers and were dropped into 6 bowls of dissolution 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±0.5$^0$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.

**2.4.2**-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 |

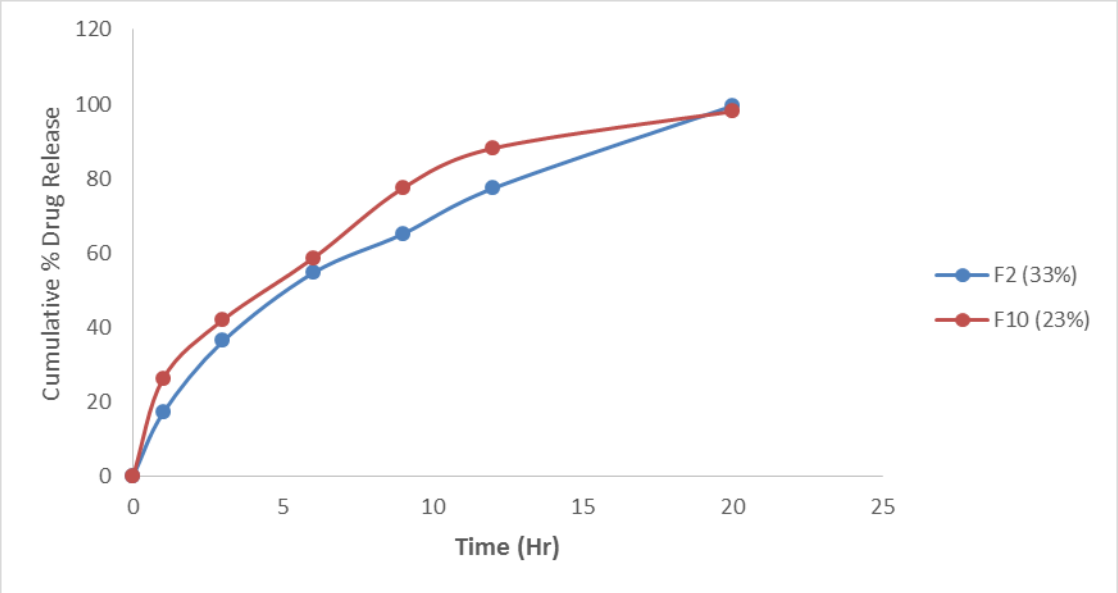



**Fig. 11: Effect of HPMC concentration on cumulative drug release profile of Metoprol Succinate MSF2-(33% HPMC), MSF10-(23% HPMC).**

**2.3.4**-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 |

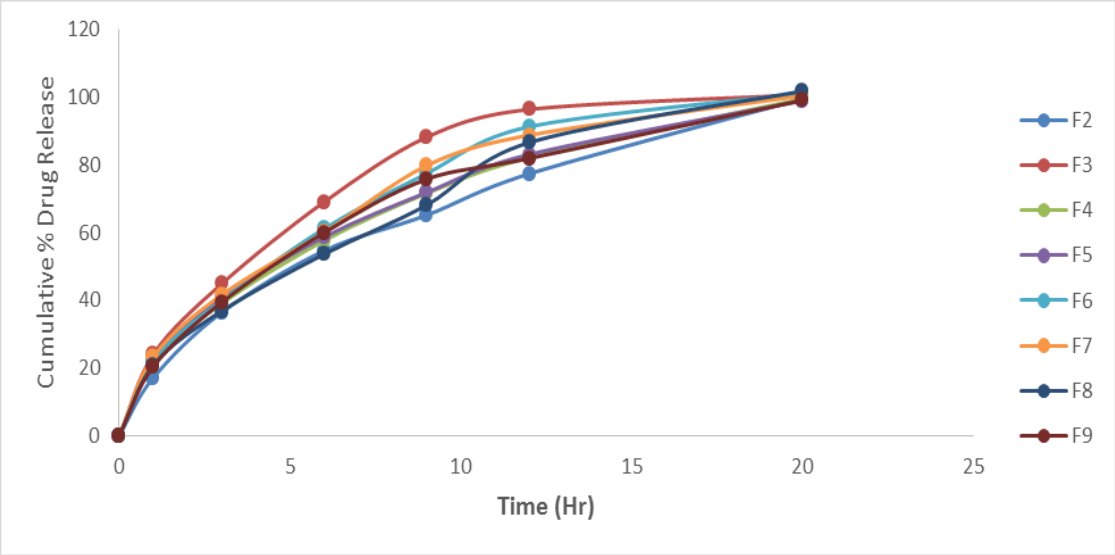



**Fig 12: Cumulative % drug release profiles of Metoprolol Succinate observed from formulations containing different polymers:[MSF2(Eudragit RSPO-40%), MSF3(SodiumCMC-35%), MSF4(Sodium Alginate-30%), MSF5 (HPC-25%), MSF6(EC-20%), MSF7(Eudragit-LPO-15%), MSF8(Eudragit-RS100-10%), MSF9(EC-10%)].**

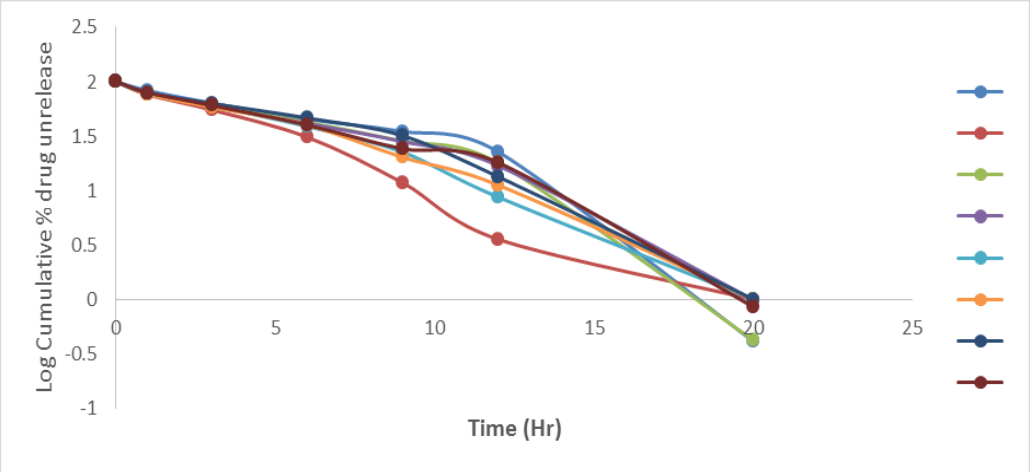



**Fig 13: First order plots of Metoprolol Succinate from formulations containing different polymers: [MSF2(Eudragit RSPO-40%), MSF3(Sodium CMC -35%), MSF4(Sodium Alginate-30%), MSF5 (HPC-25%), MSF6 (EC-20%), MSF7(Eudragit- LPO-15%), MSF8 (Eudragit-RS100-10%), MSF9(EC-10%)].**

**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.

## 3-RESULT AND DISCUSSION

### 3.1-Cummulative drug dissolution data of Sucralfate formulation

**3.1.1-** Cummulative drug dissolution data of Sucralfate formulation shows 71.42% release at 5$^{th}$ minute inacid medium (0.1HCL) in presence of 7% (Crosspovidone as Superdisintigrant). **Table-4, Table-5, Fig-1, Fig-2.**

**3.1.2-**Cummulative drug dissolution data of Sucralfate formulation shows 66.74% release at 5$^{th}$ minute in acid medium (0.1 HCL) in presence of 7% (Polysorbate-80 as Surfectant) **Table-6, Table7, Fig-3, Fig-4.**

**3.1.3-**Cummulative drug dissolution data of Sucralfate formulation shows 70.583% release at 5$^{th}$ 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.**

**3.1.4-** Cummulative drug dissolution data of Sucralfate formulation shows 65.53% release at 5$^{th}$ 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.**

**3.2-Cummulative drug dissolution data of Metoprol Succinate formulation**

**3.2.1**-Cummulative drug dissolution data of Metoprol Succinate formulation shows 99.59% release at 20$^{th}$ minute in acid medium (0.1 HCL) in presence of 30% of Sodium Bicarbonate as Alkalizing agent. **Table-13, Fig-10.**

**3.2.2**-Cummulative drug dissolution data of Metoprol Succinate formulation shows 99.46% release at 20$^{th}$ minute in acid medium (0.1 HCL) in presence of 50% of HPMC as soluble polymer. **Table-14, Fig-11.**

**3.2.3**-Cummulative drug dissolution data of Metoprol Succinate formulation shows release at 20$^{th}$ 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.**

**3.3-Result of optimization of Sucralfate layer. Table-16**

Within 5 minutes in 0.1 HCL medium, 7% Superdisintigant (Crosspovidone) produce 71.42% drug release in SF13, 7% Surfectant (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.**

| Sl NO | INGREDIENTS | MEDIUM | %OF INGRADIENTS TAKEN | TIME IN MINUTES | % OF DRUG RELEASE | FORMULATION |
|---|---|---|---|---|---|---|
| 1 | Superdisintigant (Crosspovidone) | 0.1 HCL | 7% | 5$^{th}$ | 71.42 % | SF13 |
| 2 | Surfectant (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% Soluablepolymer (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.**

| Sl NO | INGRADIENTS | MEDIUM | %OF INGRADIENTS TAKEN | TIME IN MINUTES | % OF DRUG RELEASE | FORMULATION |
|---|---|---|---|---|---|---|
| 1 | Alkalizing agent (Sodium bicarbonate) | 0.1 HCL | 30% | 20th | 99.59 % | MSF2 |
| 2 | Soluablepolymer (HPMC K) | 0.1 HCL | 50% | 20th | 99.46% | MSF2 |
| 3 | Polymer (Udragid RSPO) | 0.1 HCL | 40% | 20th | 99.59% | MSF2 |
| 4 | Polymer(NaCMC) | 0.1 HCL | 35% | 20th | 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 |

## 4-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.

## 5-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 INTREST

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

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