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DEVELOPMENT & *IN-VITRO* CHARACTERIZATION OF BI-LAYER MATRIX TABLETS OF METOPROLOL TARTARATE

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ABSTRACT

This research topic is intended to develop and characterize bilayer tablet of Metoprolol tartarate. The first layer is immediate release layer intended to produce fast therapeutic action and second layer is the sustained release layer intended to produce extended release and sustained action for a prolonged period of time. The immediate release layer is formed by taking lactose as diluent and starch as binder and disintegrating agent. The granules are formed by wet granulation technique and compressed to form first layer.The sustained release layer is formed by taking Ethyl cellulose, HPMC,lactose with PVPK30 as granulating agent. The granules are prepared by wet granulation method and again recompressed with the first layer. In the evaluation tests, preformulation studies of

immediate release layer granules and sustained release layer granules have been done. Similarly, physical characteristic evaluation of bilayer tablets has been done along with drug release profile study.At the end, it is being found that, all the formulation shows good physical characteristic and shows good drug release characteristics more 80% after 6 hours. Among all formulations, F_3 has shown good physical characteristic and better drug release than other formulations.

KEY WORDS: Bilayer Tablet, Metoprolol Tartarate, Formulation by Wet Granulation, Preformulation Studies of Granules, Physical Characteristic Evaluation of Tablets, *In-Vitro* Drug Release Profile Study.

INTRODUCTION

A bilayer tablet comprises a single layer of a single drug intended to be released immediately and another designed layer for later releasing of a same or different drug, either as a second dose or as an extended release. Generally, bilayer tablets are used for sequential release of two drugs in combination, to separate two incompatible drugs, and for sustained release tablets, where one layer is for immediate release as an initial dose, and the second layer is for maintenance (1, 2). In addition to its antihypertensive properties, Metoprolol (MPL) is a highly selective beta-1 adrenergic antagonist that does not cause any side effects on the sympathetic nervous system. Medications like Metoprolol antagonize beta 1-adrenergic receptors in the myocardium, thereby reducing the rate and force of myocardial contractions. It may also reduce renin secretion with subsequent reductions in Angiotensin-II levels, thus preventing vasoconstriction and aldosterone secretion (3 ,4).

MATERIALS AND METHODS:

MATERIALS :Metropolol MPL was obtained as a gift sample from Ipca Laboratory (Mumbai, India). DS was obtained as a gift sample from Merck Pharmaceutical (Mumbai, India). Ac-Di-Sol , Explotab and microcrystalline cellulose were obtained as a gift samples from JRS Pharma (LP Patterson, NY, USA). HPMC K100M was obtained as a gift from Colorcon (Mumbai, India). Magnesium stearate and colloidal silicone-dioxide

was obtained from S.D. Fine Chem Ltd. (Mumbai, India). All reagents used in these experiments were of analytical grade.

METHODS:

PREPARATION OF IMMEDIATE RELEASE METOPROLOL TARTARATE LAYER

All ingredients were passed through appropriate sieves such as #40 mesh and collected the individual materials in separate paperboard. 50% amount of the starch(25mg) was taken and made it to paste form properly with the help of purified water. Remaining 25mg of starch is added with Lactose properly and is mixed well with the starch paste until uniform dough mass is formed. The dough mass was passed through # 22 to get uniform sized granules. The wet granules were dried at 50-55°C temperature for10-15minutes. Then the dried granules were added with talc and magnesium stearate to mix for 2 mins. The final gnanules were compressed with us 7 mm round punch rotary tablet machine (Minipress I, Karnavati Eng, Mehsana, Gujarat, India). For all formulations, compression force was maintained at a constant level. The composition of immediately release layer is shown in Table-1(5, 6).

TABLE 1:-FORMULATION OF IMMEDIATE RELEASE LAYER

SL.NO.	INGREDIENTS	QUANTITY(mg)
1	Metoprolol Tartarate	10
2	Starch	50
3	Lactose	42
4	Talc	3
5	MagnesiumStearate	5
Total Weight		110

PREPARATION OF SUSTAINED RELEASE METOPROLOL TARTARATE LAYER

The MPL, Ethylcellulose, HPMC and Lactose are mixed well. The binder solution was preapredby dissolving PVPK30 in isopropylalcohol. After that the particle mixture is added with the viscous PVPK30.Thenthewetmassis passed through #22 to get wet granules the wet granules were dried at 60℃ 10 to15miniutes.The Magnesium Stearate and Talc is added with the final dry granules. Compress the final blend with the immediate release formulation using tablet compression machine (7, 8).

TABLE 2: PREPARATION OF SUSTAINED RELEASE LAYER

S.NO	INGREDIENTS	F1	F2	F3	F4	F5
1	MetoprololTartarate	50	50	50	50	50
2	EthylCellulose	100	150	50	125	75
3	HPMC	100	50	150	75	125
4	PVPK30	80	80	80	80	80
5	Lactose	190	190	190	190	190
6	Talc	12	12	12	12	12
7	MagnesiumStearate	8	8	8	8	8
8	**Total**	540	540	540	540	540

TABLE-3: PREFORMUALATION STUDIES ON IMMEDIATE RELEASE LAYER

GRANULES

PREFORMUALATION STUDIES ON IMMEDIATE RELEASE LAYER GRANULES			
S.NO.	**TESTS**	**F1**	**F2**
1	Bulk density (g/ml)	0.36	0.34
2	Tapped density (g/ml)	0.44	0.43
3	Hausner's ratio	1.22	1.25
4	Angle of repose (°)	25.74	25.55
5	Compressibility Index (%)	18.29	19.25

TABLE NO-4:- PREFORMUALATION STUDIES ON SUSTAINED RELEASE LAYER GRANULES

Preformualation studies on Sustained release layer granules						
S.NO.	**TESTS**	**F1**	**F2**	**F3**	**F4**	**F5**
1	Bulk density (g/ml)	0.41	0.44	0.48	0.43	0.46
2	Tapped density (g/ml)	0.50	0.51	0.53	0.51	0.52
3	Hausner's ratio	1.21	1.22	1.11	1.18	1.13
4	Angle of repose (°)	25.12	26.22	22.41	24.51	23.41
5	Compressibility Index (%)	17.80	18.20	15.50	16.40	15.90

Formulation code	WeightVariation(mg)	Hardness(kg/cm2)	Friability(%w/w)	Thickness(mm)	DT(min)
F1	650 ±0.03	5.9	0.65	3.7	120

F2	650 ±0.07	5.7	0.62	3.6	130
F3	649 ±0.09	6.0	0.69	3.8	125
F4	648 ±0.05	6.1	0.58	3.7	122
F5	650 ±0.04	6.2	0.70	3.8	130

TABLE-5: PHYSICAL CHARACTERIZATIONS OF BI-LAYER TABLETS

Time (min)	**F1**	**F2**	**F3**	**F4**	**F5**
0	0	0	0	0	0
10	4.2	11.82	3.42	4.28	3.81
30	7.9	14.78	7.03	8.08	5.58
60	11.67	16.63	14.11	13.44	11.53
120	16.96	18.93	21.45	20.86	19.22
150	24.48	23.71	25.32	24.83	27.64
180	31.68	29.28	30.98	29.28	27.94
240	32.92	34.03	36.14	33.53	33.56
300	46.11	42.83	42.43	41.47	45.58
360	47.9	44.36	50.09	45.61	46.97
420	49.67	49.7	52.51	49.28	47.44
480	53.17	52.84	55.39	52.08	50.31
600	78.12	75.62	80.12	88.35	72.31
720	80.12	88.31	85.32	96.31	89.35

TABLE-6:-DRUG RELEASE PROFILE

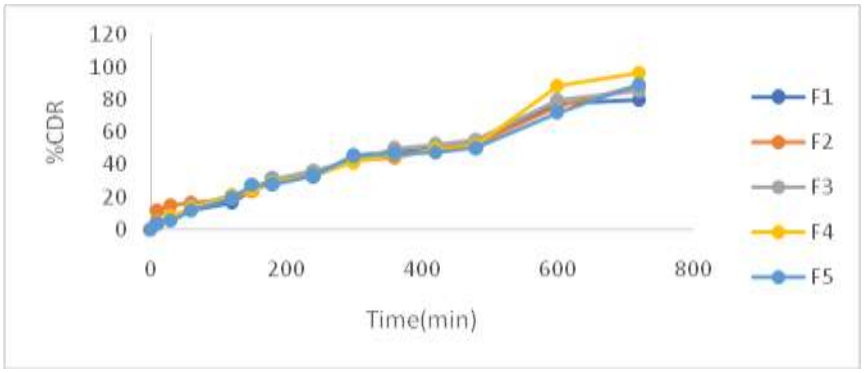

FIGURE-1:-DRUG RELEASE PROFILE

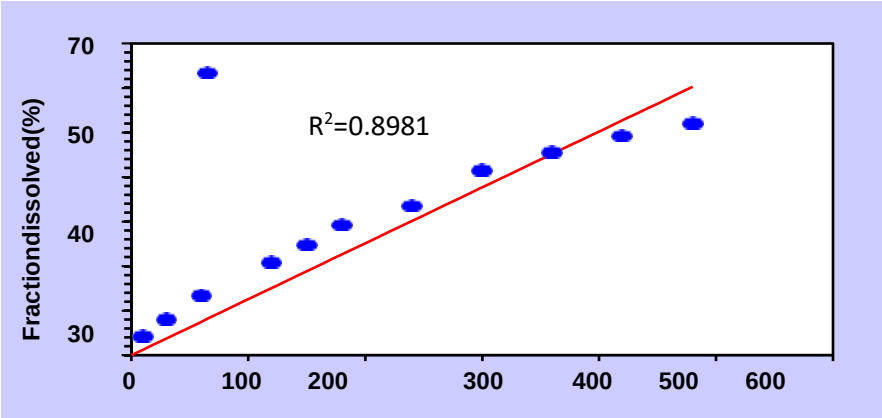

FIGURE 2: DISSOLUTION DATA MODELING OF ZERO-ORDER MODEL

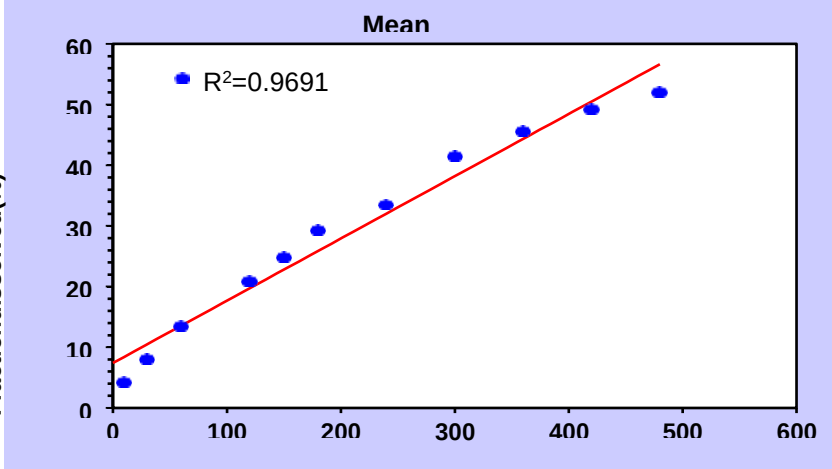

FIGURE 3:DISSOLUTION DATA MODELING OF FIRST-ORDERMODEL

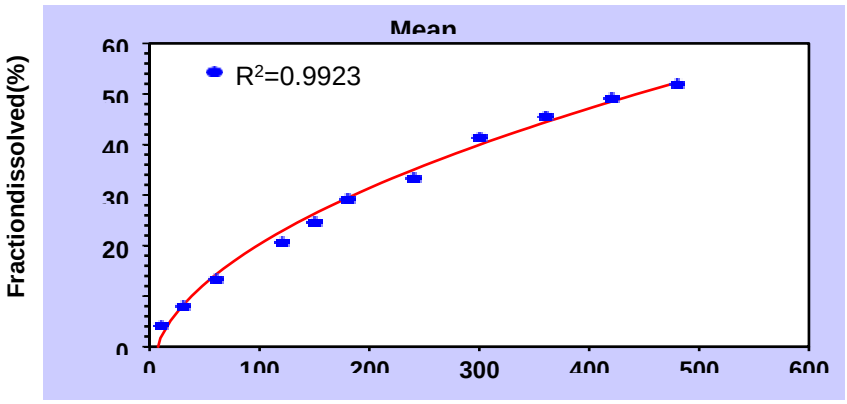

FIGURE 4:DISSOLUTIONDATAMODELINGOFHIGUCHIMODEL

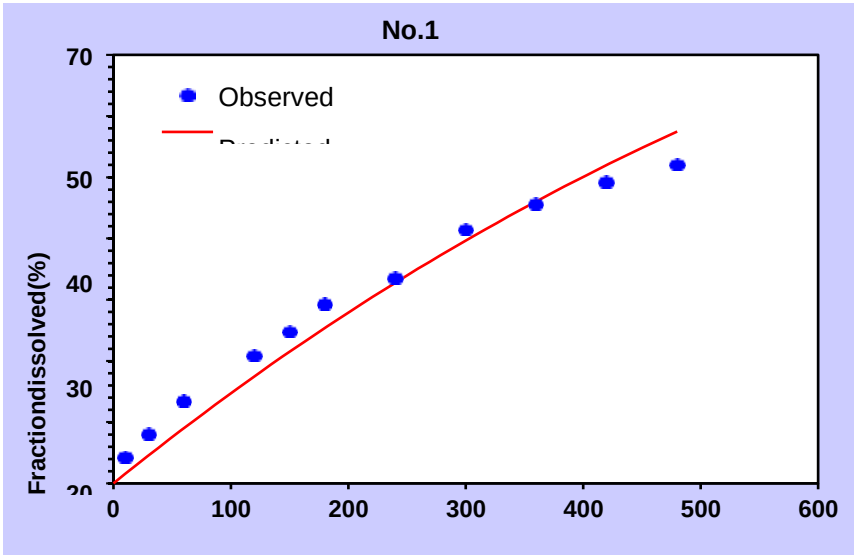

FIGURE 5:DISSOLUTIONDATAMODELINGOFHIXON-CROWELLMODEL

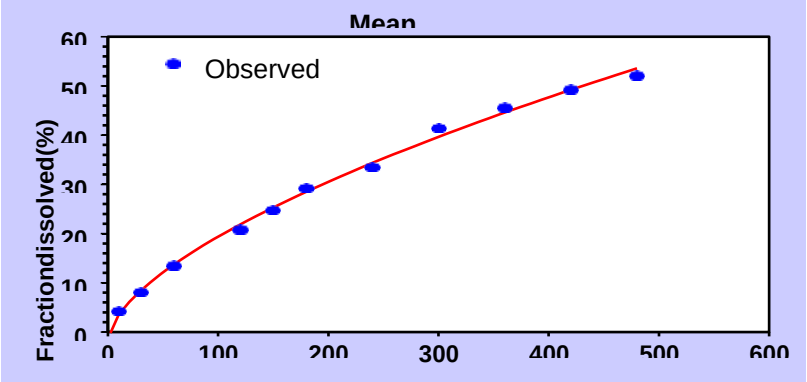

FIGURE 6: DISSOLUTIONDATAMODELINGOFKORSMEYER-PEPPAS MODEL

RESULTS AND DISCUSSION:

The Bilayer Tablet of Metoprolol Tartarate was evaluated for various parameters.Granules are generally known to possessbetterflowpropertiesthanpowderedmaterials. The angles of repose of all formulations are found out between 25-26˚ which can be shown in Table-3 and 4. Angle of repose is used to determine the flow ability of powdered materials; values between 21 - 35 are generally considered suitable. Bulk densities of the granules and powdered mixtures are 0.34 to 0.36 grams/ml and 0.41 to 0.46 grams/ml, respectively for immediate release and sustained release formulations. For immediate release granules, the tapped density is 0.4-0.44 g/ml and for sustained release granules, it is 0.5-0.52 g/ml, as can be seen in Tables 3 and 4.A high bulk density for powdered materials is good because of increased fill weight achieved.

According to Table 3-4, the Hausner's Ratio values obtained for the granules and powdered mixtures are 1.11-1.25, which indicates proper flow. High values may be due to interparticulate friction which impedes flow.

Table No. 5 shows the physical properties of bilayer matrix tablets. Weight uniformity tests were passed by all batches of tablets. Standard deviations from the mean weight are low. Each batch of tablets shows little variation in weight. Hardness of tablets was 4-

5kg/cm. Friability was 0.58-0.70%. Five formulations are evaluated and various models are prepared. As a result, it was found that formulation 3(F3) had better dissolution characteristics. Similarly after comparing with other formulations, Formulation 3 (F3) has better drug release from the matrix design data and is the best suitable formulation than others as per Table-6.

CONCLUSION:

Ordinarily, conventional dosage forms produce wide ranging variations in drug concentrations in the blood and tissues, resulting in undesirable toxicity and poor efficacy. As a result of repetitive dosing and unpredictable absorption, controlled drug delivery systems were developed. Designing sustained or controlled delivery systems aims to minimize the frequency of dosing or to increase the effectiveness of the drug by locating it at the target site, reducing the dose or providing uniform distribution. Drugs delivered by sustained release are intended to ensure patient safety, improve efficacy, as well as increase compliance with their treatment. Bi-layer tablet is suitable for sequential release of two or one drug, in which one layer is immediate release while the other layer is sustained release. The sustained release layer is formulated by matrix technique. Matrix technique is gaining an importance in current days as a simplest technique for a controlled release of drugs. Metoprolol tartarate loaded Bilayer matrix tablet was successfully prepared by developing the formulation using matrix design. Here conclude that it shows maximum percentage of drug release. The immediate release and the sustained release are studied by dissolution method and it shows above 80% drug release after 6hours of study.

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