



DESIGN FORMULATION AND EVALUATION OF GASTRORETENTIVE DRUG DELIVERY SYSTEM: A RESEARCH

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ABSTRACT

Metoprolol succinate sustained release tablet is a beta-1 (cardio-selective) adrenoceptor- blocking agent formulated to provide controlled and predictable release of metoprolol. The pharmacokinetics, efficacy, and safety/tolerability of the antihypertensive combination tablet, essentially reflect the well-described independent characteristics of each of the component agents. The aim of present work was to develop a robust formulation of Metoprolol Succinate sustained Release matrix tablets. The drug product developed to reduce Hypertension. Metoprolol Succinate is an antihypertensive (cardio selective b-blocker) used in the management of hypertension, angina pectoris and heart failure in doses ranging from 25 mg to 200 mg. It is most widely used drug for the treatment of hypertension in USA and America.

KEYWORDS: Antihypertensive drug, sustained release tablets, polymers, Hypertension.

HYPERTENSION

Hypertension^[1] is a chronic medical condition in which the blood pressure in the arteries is elevated. It is classified as either primary (essential) or secondary. About 90-95% of cases are termed primary be found and for remaining fraction of cases the causes are known like hyperlipidimia etc. Hypertension effects almost all organs of the body like kidneys, arteries, heart, or endocrine system. Hence, there is growing need for development of suitable medication to treat or manage hypertension. Anti-hypertensive are class of drugs which are used to manage hypertension. There are various classes of drugs which are used as antihypertensive like beta blockers, calcium channel blockers; ACE inhibitors etc., among all these, beta blockers are still being used as first line agents used for management of hypertension. Metoprolol succinate.^[2] is a beta1-selective (cardio selective) adrenergic receptor blocking agent. This preferential effect is not absolute, however, at higher plasma concentrations, Metoprolol succinate also inhibits beta2-adrenoreceptors, chiefly located in the bronchial and vascular musculature. Metoprolol succinate has no intrinsic sympathomimetic activity and membrane-stabilizing activity is detectable only at plasma concentrations much greater than required for beta-blockade. Because of these desired pharmacodynamic properties, Metoprolol succinate is used popularly for management of hypertension. Metoprolol succinate belongs to class I category in BCS classification system, i.e. freely soluble & highly permeable. Because of good solubility and permeability, its bioavailability is more

and half life is less.

This results in multiple doses of Metoprolol succinate every day. Hence, continuous efforts are being made whereby number of doses of Metoprolol succinate can be minimized. This has resulted in formulation of Metoprolol succinate in to extended release form. Literature is flooded with reference in which various approaches are used for the formulation of extended release form of Metoprolol. These methods suffer from one or the other disadvantages. Hence, in the present work an attempt will be made in which formulation of Metoprolol succinate will be designed for extended release and it will be validated.^[3] This reduces the volume of the blood, decreasing blood return to the heart and thus cardiac output and, by other mechanisms, is believed to lower peripheral vascular resistance.^[4]

Introduction To Sustained Release Tablets

Oral ingestion.^[5,6,7] has long been the most convenient and commonly employed route of drug delivery due to its ease of administration. It is well known that modified release dosage forms may offer one or more advantages over immediate release formulations of the same drug. There are many ways to design modified release dosage forms for oral administration; from film coated pellets, tablets or capsules to more sophisticated and complicated delivery systems such as somatically driven systems, systems controlled by ion exchange mechanism, systems using three dimensional printing technology and systems using electrostatic deposition technology. The design of

modified release drug product is usually intended to optimize a therapeutic regimen by providing slow and continuous delivery of drug over the entire dosing interval whilst also providing greater patient compliance and convenience.^[8,9] The most common controlled delivery system has been the matrix type such as tablets and granules where the drug is uniformly dissolved or dispersed throughout the polymer, because of its effectiveness, low cost, ease of manufacturing and prolonged delivery time period.^[10] Usually conventional dosage form produce wide ranging fluctuation in drug concentration in the blood stream and tissues with consequent undesirable toxicity and poor efficiency. This factor such as repetitive dosing and unpredictable absorption led to the concept of controlled drug delivery systems. The primary objective of sustained release drug delivery is to ensure safety and to improve efficacy of drugs as well as patient compliance.^[11] There is various application of the bi-layer tablet it consist of monolithic partially coated or multilayered matrices. In the case of bi-layered tablets drug release can be rendered almost unidirectional if the drug can be incorporated in the upper non-adhesive layer its delivery occurs into the whole oral cavity.^[12]

Methods of Granulation

Granulation is the act or process of forming or crystallizing into small particles. Granules typically have a size range between 0.2 to 4.0 mm depending on their subsequent use. The granulation process combines one or more powder particles and forms a granule that will allow tableting or spheronization process to be within required limits. This way predictable and repeatable process is possible and quality tablets or pellets can be produced using tableting or spheronization equipment.^[13,14,15]

Granulation is carried out for various reasons, one of those is to prevent these aggregation of the constituents of powder mix. Segregation is due to differences in the size or density of the component of the mix. Normally, the smaller and/or denser particles tend to concentrate at the base of the container with the larger and/or less dense ones on the top. An ideal granulation will contain all the constituents of the mix in the correct proportion in each granule and segregation of granules will not occur. Many powders, because of their small size, irregular shape or surface characteristics, are cohesive and do not flow well. Granules produced from such a cohesive system will be larger and more isodiametric, both factors contributing to improved flow properties. Some powders are difficult to compact even if a readily compactable adhesive is included in the mix, but granules of the same powders are often more easily compacted. This is associated with the distribution of the adhesive within the granule and is a function of the method employed to produce the granules.^[16,17,18]

Granulation Techniques

In pharmaceutical industry, two types of granulation

technologies are employed, namely, wet granulation and dry granulation.

Wet Granulation

In wet granulation, granules are formed by the addition of a granulation liquid onto a powder bed which is under the influence of an impeller (in a High shear granulator, screws (in a twin screw granulator) or air (in a fluidized bed granulator). The agitation resulting in the system along with the wetting of the components within the formulation results in the aggregation of the primary powder particles to produce wet granules. The granulation liquid (fluid) contains a solvent which must be volatile so that it can be removed by drying, and be non-toxic. Typical liquids include water, ethanol and isopropanol either alone or in combination. The liquid solution can be either aqueous based or solvent based. Aqueous solutions have the advantage of being safer to deal with than solvents.^[19,20,21] Water mixed into the powders can form bonds between powder particles that are strong enough to lock them together. However, once the water dries, the powders may fall apart. Therefore, water may not be strong enough to create and hold a bond. In such instances, a liquid solution that includes a binder (pharmaceutical glue) is required. Povidone, which is a polyvinyl pyrrolidone (PVP), is one of the most commonly used pharmaceutical binders. PVP is dissolved in water or solvent and added to the process. When PVP and a solvent/water are mixed with powders, PVP forms a bond with the powders during the process, and the solvent/water evaporates (dries). Once the Solvent/water has been dried and the powders have formed a more densely held mass, then the granulation is milled. This process results in the formation of granules. The process can be very simple or very complex depending on the characteristics of the powders, the final objective of tablet making, and the equipment that is available. In the traditional wet granulation method the wet mass is forced through a sieve to produce wet granules which is subsequently dried.^[22,23,24]

Dry Granulation

The dry granulation process is used to form granules without using a liquid solution because the product to be granulated may be sensitive to moisture and heat. Forming granules without moisture requires compacting and densifying the powders. In this process the primary powder particles are aggregated under high pressure. Swaying granulator or high shear mixer-granulator can be used for the dry granulation.^[25, 26] Dry granulation can be conducted under two processes; either a large tablet (slug) is produced in a heavy duty tableting press or the powder is squeezed between two rollers to produce a sheet of materials (roller compactor, commonly referred to as a chilsonator). When a tablet press is used for dry granulation, the powders may not possess enough natural flow to feed the product uniformly into the die cavity, resulting in varying degrees of densification. The roller compactor (granulator-compactor) uses an auger-feed system that will consistently deliver powder uniformly

between two pressure rollers. The powders are compacted into a ribbon or small Pellets between these rollers and milled through a low-shear mill. When the product is compacted properly, then it can be passed through a mill and final blend before tablet compression.^[27]

Tablets by Direct Compression

Direct Compression is by far the easiest means of processing tablets, because it only involves the main steps of powder blending, lubrication and compaction. Because there is no granulation step to improve flow and compaction it is usually necessary to use excipients specifically designed for direct compression, and engineered to provide the necessary flow and compaction properties. Such materials are sometimes known as “filler-binders”. Despite the availability of these materials, the utility of direct compression may be limited by the dose of drug to be tableted.

Importance of The Present Metoprolol Succinate

The aim of present study is to develop a sustained release tablet for management of Hypertension using and Metoprolol succinate. The sustained release tablets are prepared using different viscosity grades of hydrophilic polymers for sustained released tablets, prepared tablets are evaluated for their physico-chemical properties. Bilayer tablet technology has been specially developed to provide two different release rates or biphasic release of a drug from a single dosage form. For these types of drugs, extended release formulations generally lead to a delayed appearance of effective plasma levels and they cannot provide a prompt disposition of the dose, while the immediate released formulation appears quickly after their administration. Combination drug therapy is recommended for treatment of hypertension to allow the

medications of different mechanism of action to complement each other and together effectively lower blood pressure at lower than maximum doses of each. The rationale for combination therapy is to encourage the use of lower doses of drug to reduce the patient's blood pressure to achieve the goal to minimize dose dependent side effects and adverse reactions. When smaller doses of medication with different mechanism of action are combined, synergistic or additive effects on blood pressure are achieved and dose dependent side effects are minimized. Metoprolol succinate is from BCS class 1. Thus this poorly soluble compounds leads to high intra- and inter-subject variability and lack of dose proportionality and it resulting fluctuation in dosing with conventional dosage form. Thus the strong need for the development of sustained release tablets is recognized to deliver loading dose of drug in the stomach, to reduce frequency of administration and to increase the efficacy of the drug by providing sustained action.^[28,29] In the present study, a combination drug therapy of HCTZ and Metoprolol succinate is recommended for treatment of hypertension to allow medications of different mechanism of action to complement each other and together effectively lower blood pressure at lower than maximum doses. Therapy with any combination of Metoprolol succinate extended release and Hydrochlorothiazide will be associated with both sets of dose independent side effects.

MATERIALS AND METHODS

Materials

Metoprolol succinate was purchased from the Yarrow Pharma. HPMC K100M, HPMC K4 M was purchased from the S.D fine Chem Ltd, India. All the chemicals used was of an analytical grade

METHOD

Table 1: Composition of Sustained Release Tablets.

Sr. No	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Metoprolol Succinate	47.5	47.5	47.5	47.5	47.5	47.5	47.5	47.5	47.5
2	HPMC K100M	47.5	95	142.5	47.5	95	142.5			
3	Ethyl Cellulose	27.5	27.5	27.5				27.5	27.5	27.5
4	HPMC K4M				27.5	27.5	27.5			
5	Magnesium Stearate	3	3	3	3	3	3	3	3	3
6	Talc	2	2	2	2	2	2	2	2	2
7	Total Weight Of The Tablet(Mg)	127.5	175	222.5	127.5	175	222.5	127.5	175	222.5

Results and DiscussionPreformulation Studies

1.1 Solubility Determination

Metoprolol Succinate is freely soluble in water; soluble in methanol; sparingly soluble in ethanol; slightly soluble in dichloromethane; practically insoluble in ethyl acetate, acetone, diethylether.

Melting point determination

Metoprolol has a very low melting point around 136°C.

1.2 IR Spectroscopy

The IR spectrum of Metoprolol Succinate pure drug was found to be similar to the standard spectrum of Metoprolol Succinate as in IP. The spectrum of Metoprolol succinate showed the following functional groups at their frequencies. Standard spectra of drugs were shown in following tables.

1.3 Compatibility Studies

This work exemplifies a general method of studying the drug excipient interactions, with the aim of predicting

rapidly and inexpensively the long term stability of their mixtures. We study the physico-chemical properties of a drug (Metoprolol Succinate) in the solid state and in different combinations with several excipients (HPMC, Ethyl Cellulose). We compare the properties of pure compounds (untreated, or moisture/temperature conditioned) with those of binary mixtures drug: excipient which underwent the same treatment. The

purpose is to find indications of interactions within the mixtures, which means a potential incompatibility of the excipient. Both morphological and thermal properties are sensitive to interactions which leave mostly unmodified the IR spectra and the X-rays patterns. In particular, we find that Metoprolol Succinate does not interact with either HPMC or Ethyl Cellulose.

Table 2: FTIR of metoprolol succinate.

Functional groups	Wave number cm^{-1}
OH	3415.97 stretching
NH	1560.67 bending
-O-	1383.42 stretching
Aromatic ring	2930.28 stretching 639.53 bending

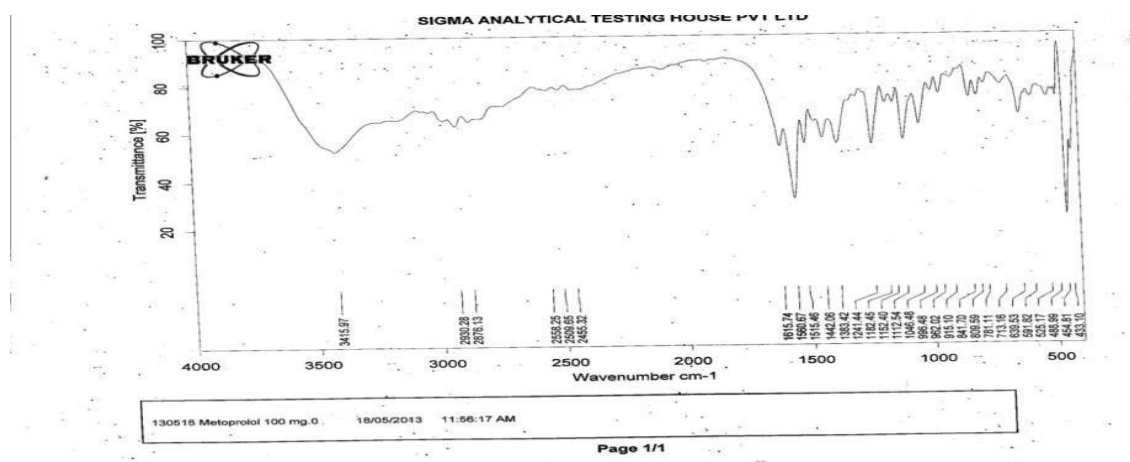


Figure 1: FT-IR studies of Metoprolol succinate.

Table 3: Metoprolol Succinate + HPMC K100M.

Functional groups	Wave number cm^{-1}
OH	3431.41 stretching
NH	1559.82 bending
-O-	1387.27 stretching
Aromatic ring	2929.34 stretching 639.68 bending

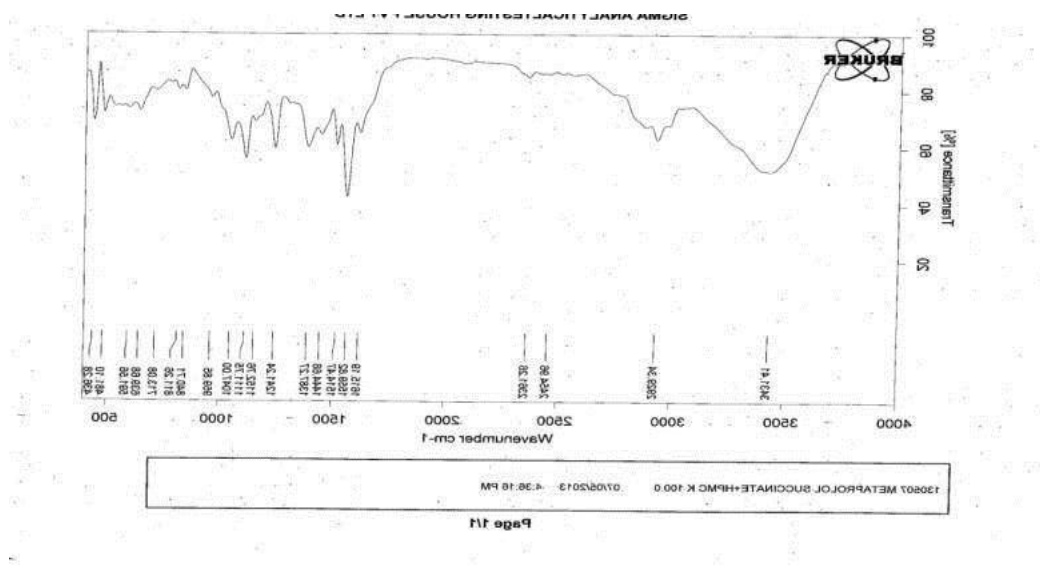


Figure 2: FT-IR studies of Metoprolol succinate+HPMC K100M.

Table 4: metoprolol succinate + Ethyl cellulose.

Functional groups	Wave number cm-1
OH	3448.12 stretching
NH	1560.25 bending
-O-	1392.85 stretching
Aromatic ring	2977.53 stretching 639.56 bending

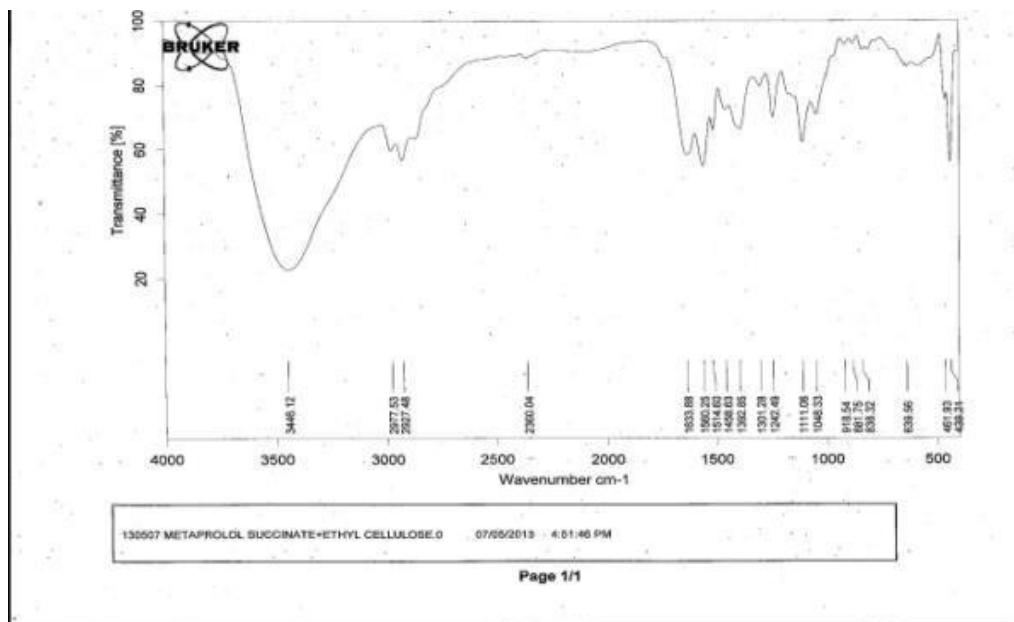
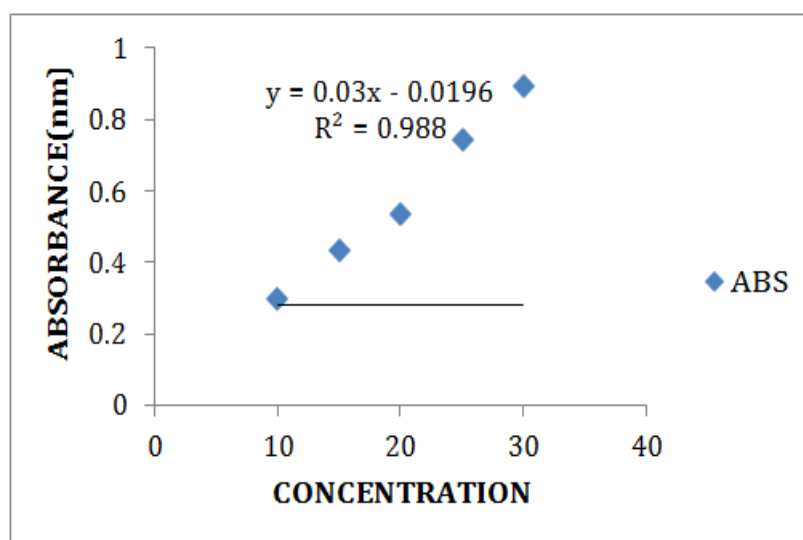


Figure 3: FT-IR studies of Metoprolol succinate+Ethylcellulose.

Determination of absorbance maximum of Metoprolol Succinate in 6.8 pH. Buffer and Standardization Metoprolol Succinate in 6.8 pH buffer

Absorbance of the drug solutions containing 10-30ppm of Metoprolol Succinate in phosphate buffer 6.8 was

shown in the table. The calibration curve was found to be in the range of 10-30ppm at 222nm with slope, regression of 0.03, 0.988.

Figure 4: Standard curve of Metoprolol succinate in 6.8P^H buffer.

Metoprolol Succinate in 0.1N HCl

Standard solution of Metoprolol succinate (10µgm/ml) was scanned in the range of 200-400nm and showed

maximum absorbance at 222nm. Absorbances of the drug solutions containing 10-30ppm of Metoprolol Succinate in 0.1N HCl was shown in the table. The

calibration curve was found to be in the range of 10-30ppm at 222nm with slope, regression of 0.0212, 0.997.

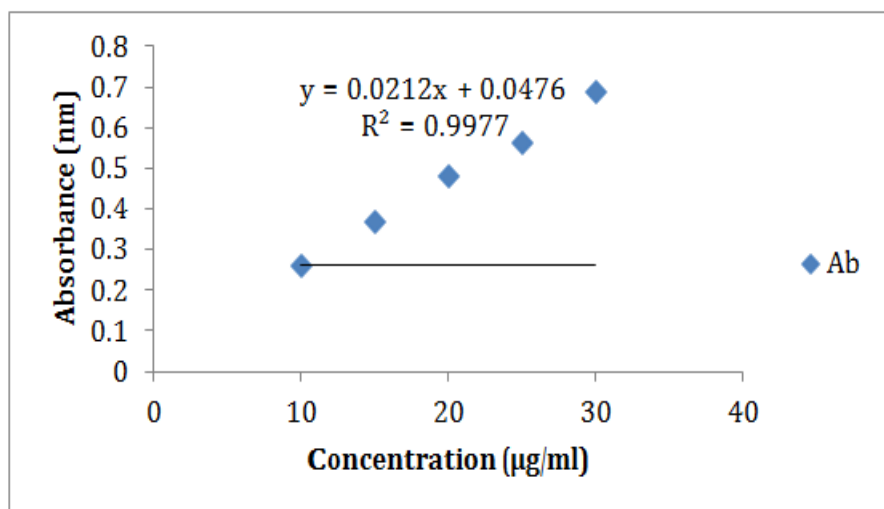


Figure 5: Standard curve of Metoprolol succinate in 0.1 HCl.

Table 5: Preformulation values of Metoprolol succinate.

Formulations (Metoprolol Succinate)	Bulk Densitygm/ml	Tapped Density gm/ml	Compressibility Index (%) (5-25)	Hausner's Ratio (1-1.6)	Angle OF Repose (θ) (25-65)
F1	0.554	0.678	18.367	1.225	23.72
F2	0.534	0.633	15.63	1.184	19.29
F3	0.569	0.68	16.279	1.194	24
F4	0.595	0.677	12	1.136	22.5
F5	0.597	0.66	9.54	1.105	21.6
F6	0.636	0.777	18.14	1.221	27.8
F7	0.462	0.806	42.6	1.744	26
F8	0.51	0.806	42.6	1.58	27.2
F9	0.518	0.611	15.217	1.179	22.4

Table 6: Post formulation values

Formulations	Hardness (kg/sqcm)± SD	Friability (%)	Weight Variation(mg)	Assay (%)
F1	4.0±0.17	0.4	179.5	96.5
F2	4.5±0.17	0.41	225	98.01
F3	4.5±0.12	0.27	272.8	98.5
F4	4.5±0.15	0.49	180	96
F5	4.0±0.12	0.45	227.5	97.89
F6	5±0.18	0.21	276	98.03
F7	4.5±0.15	0.39	178.3	97.02
F8	5.0±0.15	0.31	227.5	97.7
F9	4.0±0.16	0.29	276.9	92.8

Table 7: Dissolution Data (Metoprolol Succinate) Percentage drug release (In hrs.)

TIME	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	12.7	15	13.6	13.2	14.6	15.8	17.4	14.5	11.2
4	38.2	41.4	39.8	38.4	40.6	42	45.4	40.9	37.5
8	56	61.6	58.1	57.6	61.3	63.7	67.6	59.6	56.5
10	67.8	81.3	74.6	70.12	74.9	80.4	82.9	80.4	76.6
12	92	99.8	94.3	88	95.6	99.9	98	90.9	86

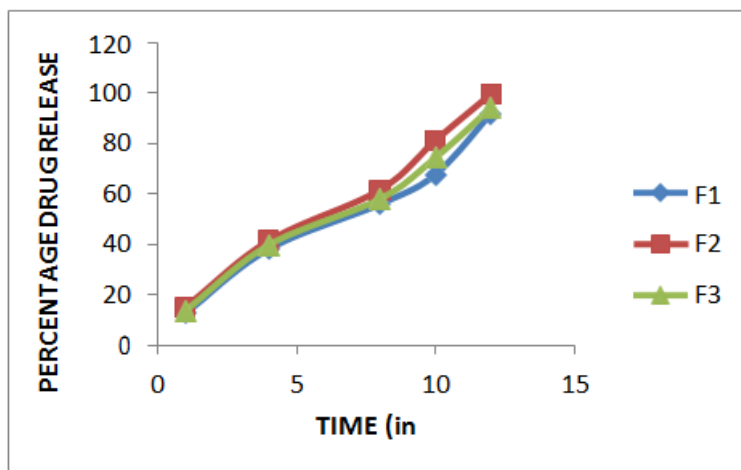


Figure 6: Time Vs. % drug release of F1, F2, F3.

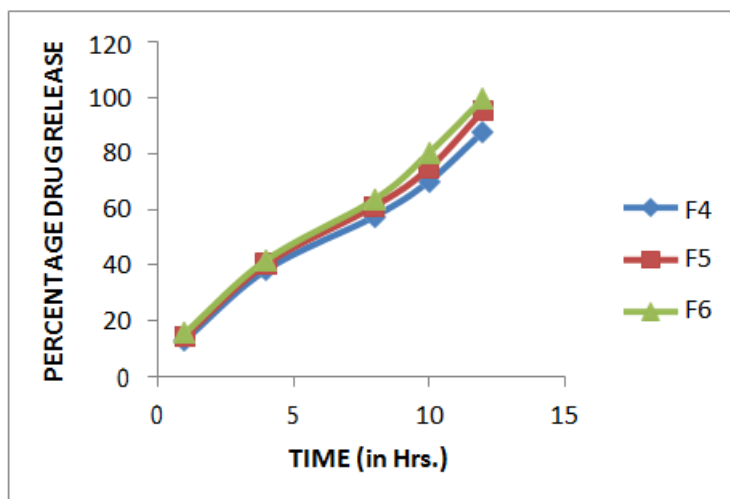


Figure 7: Time Vs. % drug release of F4, F5, F6.

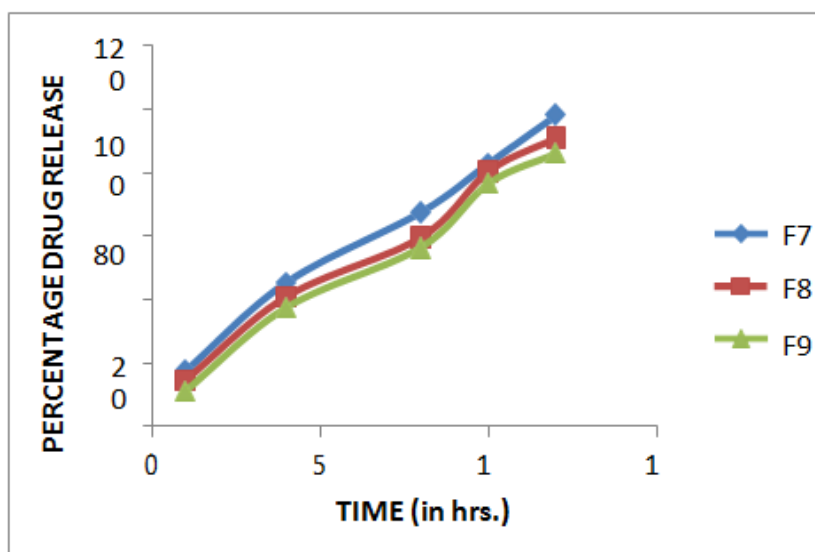


Figure 8: Time Vs. % drug release of F7, F8, F9.

4.8 Kinetic Profile

Table 8: Zero order kinetics- %Drug release versus Time (Metoprolol succinate).

Time (hrs.)	F2(%DR)	F6(% DR)	F7(%DR)
1	15	15.8	17.4
4	41.4	42	45.4
8	61.6	63.7	67.6
10	81.3	80.4	82.9
12	99.8	99.9	98

Table 9: First order kinetics-log (100-%Drug release) versus Time.

Time (hrs.)	F2 log(100-%DR)	F6 log(100-%DR)	F7 log(100-%DR)
1	1.929	1.925	1.916
4	1.76	1.76	1.73
8	1.584	1.559	1.51
10	1.271	1.292	1.232
12	-0.69	-1	0.301

Table 10: Higuchi plot- $\sqrt{\text{Time}}$ Verses % Drug release.

$\sqrt{\text{Time}}(\text{hrs})$	F2(%DR)	F6(%DR)	F7(%DR)
1	15	15.8	17.4
2	41.4	42	45.4
2.828	61.6	63.7	67.6
3.162	81.3	80.4	82.9
3.464	99.8	99.9	98

Table 11: Hixson Crowell plot- $\sqrt[3]{(100-\% \text{Drug release})}$ versus Time.

TIME (hrs.)	F2 $\sqrt[3]{(100-\% \text{DR})}$	F6 $\sqrt[3]{(100-\% \text{DR})}$	F7 $\sqrt[3]{(100-\% \text{DR})}$
1	4.39	4.38	4.35
4	3.88	3.87	3.79
8	3.37	3.31	3.18
10	2.65	2.69	2.57
12	0.58	0.46	1.25

Table 12: Korsmeyer Peppas equation-log Time versus log % Drug Release.

Log Time	F2(log%DR)	F6(log%DR)	F7(log%DR)
0	1.176	1.198	1.240
0.602	1.617	1.623	1.657
0.903	1.789	1.804	1.829

DISCUSSION

Evaluation of Tablets

The formulation consists sustained release matrix tablets of Metoprolol succinate. Developed trials were taken and evaluated for pre compression and post compression parameters of sustained release matrix tablet.

Sustained release of Metoprolol succinate

In the present study, the release extended layer of Metoprolol succinate was designed with the dose of 181.5mg, 229mg, and 276.5mg. The granules were prepared by direct compression techniques technique using HPMC as binder. HPMC K100M and HPMC K4M were used as drug release retardants for extended release layer of Metoprolol succinate, microcrystalline cellulose was used to balance the weight of the tablet. The weight of Metoprolol succinate layer for all formulations was kept constant at 47.5mg. Bulk Density and tapped density for Metoprolol succinate extended release granules were found to be between 0.462 to 0.636 and 0.611 to 0.806

respectively. Compressibility index and Hausner's ratio were obtained in the range of 12 to 42.6 and 1.105 to 1.744 respectively. Angle of repose was observed in the range of 19°29' to 27°8'. In vitro dissolution study of the formulation containing polymer in different concentration were compared. In formulation, F - 1 to F - 3 the ER layer consist of HPMC K100M and Ethyl cellulose, F - 4 to F - 6 the ER layer consist of HPMC K100M and HPMC K4M, and the weight of the tablet was balanced with Microcrystalline cellulose. The release of drug in F - 2 & F - 6 was found to be within the internal specification limit. F7 to F9 consists of kollidone & EC and F10 to F12 consists of kollidone & HPMC K4M.

Dissolution

The drug release of F2, F6, F7, at the end of 12th hour was found to be 99.8%, 99.9%, 98%, 99.5% for Metoprolol succinate. The drug release of optimized formulations were found to be increased when compared with the standard drug.

Release kinetics study for optimized sustained release matrix tablets of metoprolol succinate.

The kinetics of drug release was determined based on

Korsmeyer - Peppas equation obtained by in vitro dissolution data to various kinetics models. Accordingly the R^2 value of F2, **F6**, **F7**, were found to be 0.9874, **0.9903**, **0.993**, **0.9923** respectively for Zero order.

Table 13: R^2 values.

Formulation	R^2	R^2	R^2	R^2	R^2	
	Zero order	First order	Higuchi	Hixon crowell	Korsmeyer peppas	N
F2	0.9874	0.798	0.9607	0.8006	0.9966	0.6865
F6	0.9903	0.8774	0.9644	0.7884	0.9985	0.6761
F7	0.993	0.776	0.985	0.9028	0.9979	0.658
F11	0.9923	0.6686	0.9733	0.8435	0.9989	0.677

From the above results and discussions, I have observed that F-6 was found to be optimized and has passed the

prescribed limits for pre and post for formulation studies with a dissolution rate of 99.9%.

Table 14: Data of optimized formulation F-6.

Preformulation studies	Metoprolol succinate
Bulk density(gm/ml)	0.56
Tapped density(gm/ml)	0.6
Carr's index (%)	14.8
Hausner's ratio	1.1
Angle of response($^{\circ}$)	27.8
Post formulation studies	
Hardness(kg/cm ²)	5
Friability (%)	0.21
Weight variation	276
Dissolution (%)	99.9
Kinetic profile	
Zero order	0.9903
First order	0.8774
Higuchi equation	0.942
Hixon Crowell equation	0.992
Korsmeyer-peppas equation	0.998(n =0.6761)

CONCLUSION

Metoprolol succinate of metoprolol succinate tablets lower blood pressure in hypertensive patients. The blood pressure reductions are dose related and represent additive antihypertensive contributions from the component agents. The likelihood of controlling elevated blood pressure with the combination product is greater than with the component agents employed as immunotherapies, even in patients with more severe levels of hypertension. The combination also provides an option to treat with lower doses of the individual agents. Metoprolol succinate is generally well tolerated, reflecting the characteristics of the components, but it also reflects the same safety profiles including the admonition to avoid abrupt cessation of treatment in patients with or at risk for underlying coronary artery disease. Physicians might also consider that low dose combination products provide an option to intervene with well-tolerated treatments early in the course of hypertension and might well help patients avert more intractable hypertension. It included about the hypertension disease profile, description about the drugs Metoprolol succinate and knowing about tablet dosage

form and advantages of bilayer tablets over conventional dosage form, importance of present combination and objective of present project. It shows the abstracts of different articles and journals collected in order to give an idea for the present title, done including selection of raw materials, compatibility studies, Preformulation studies, manufacturing of sustained release tablet, post formulation studies, invitro dissolution, kinetic profiles etc. the results obtained such as values of Preformulation studies, post formulation studies, values and graphs of dissolution data, zero & first order kinetics, Higuchi, Hixon-crowell, Korsmeyer and Peppas plots and regression values of the kinetics studies.

REFERENCES

1. European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. J Hypertension, 2003; 21: 1011-1053.
2. Bakris GL, Fonseca V, Katholi RE, et al. Metabolic effects of Carvedilol vs. metoprolol in patients with type 2 diabetes mellitus and hypertension. JAMA, 2004; 292: 2227-36.

3. Beermann B, Groschinsky-Grind M, Rosen A. Absorption, metabolism, and excretion of hydrochlorothiazide. *Clin Pharmacol and Thera*, 1976; 19: 531–7.
4. Nandita GD, Sudip KD. Controlled-release of oral dosage forms, *Formulation, Fill and Finish* 2003; 10-16.
5. Nagaraju, R., Rajesh kaza., *IJPS*, 2009; 2(3): 638-946.
6. Remya P.N., Damodharan, N., Sulakshan Kumar C.V., *International Journal of Pharm Tech Research*, 2010; 2(2): 1250-1255.
7. Jadhav, R.T., Payal, H., Patil and Pratibha, R. Patil., *J. Chem. Pharm. Res.*, 2011; 3(3): 423.
8. Wilding IR, Coupe AJ, Davis SS. The role of gamma scintigraphy in oral drug delivery. *Adv. Drug Deliv. Rev.*, 1991; 7: 87–117.
9. Chien YW. Fundamentals of controlled-release of drug administration in: J. Swarbrick (Ed.), *Novel Drug Delivery System* Marcel Dekker, New York, 1982; 465–574.
10. Lee L. Diffusion-controlled matrix systems, in: A. Kydonieus (Ed.), *Treatise on Controlled Drug Delivery*, Marcel Dekker, New York, 1992; 155–198.
11. Kumar KK, Mahesh M, Sasikanth K. Design, development and characterization of sustained release of Metformin hydrochloride and Gliclazide bilayered tablets by wet granulation method. *Int J Biopharm*, 2010; 1(2): 67-71
12. Shiyani B, Gattani S, Surana S. Formulation and evaluation of bi-layer tablet of Metoclopramide hydrochloride and Ibuprofen. *AAPS Pharm Sci Tech*, 2008; 9(3): 818-27.
13. Deshpande RD, Gowda DV, Mohammed N, Deepak N. Maramwar. Bi-layer tablets- An emerging trend: a review. *IJPSR*, 2011; 2(10): 2534-2544.
14. Panchal HA, Tiwari AK. Novel Approach of Bilayer tablet Technology: An Review. *Journal of Pharmaceutical Science and Technology*, 2012; 4(4): 892–904.
15. Divya A, Kavitha K, Kumar MR, Dakshayani S, Jagadeesh SSD. Bilayer tablet technology: An overview. *Journal of Applied Pharmaceutical Science*, 2011; 01(08): 43-47.
16. Patel M, Ganesh NS, Kavitha, Tamizh M. Challenges in the formulation of bilayered tablets: A review. *IJPRD*, 2010; 2(10): 30–42.
17. Panchal HA, Tiwari AK. Novel Approach of Bilayer tablet Technology: An Review. *Journal of Pharmaceutical Science and Technology*, 2012; 4(4): 892–904.
18. Aithal KS et al., 1996; Akihiko I. et al, 1996.
19. Siepmann J. et al 2001; Fausett H. et al, 2002.
20. Podczek F. et al., 2008; Aithal KS et al., 1996.
21. Rajabi AR. et al 2004; Lauretta M. et al., 1999; Huber HE et al., 1996.
22. Vyas SP. Et al, 2002.
23. Huber HE et al., 1996.
24. *International Journal of Pharmatech Research*, Apr 2009; 1(2): 159.
25. Matrix type transdermal drug delivery systems of metoprolol tartrate: in vitro characterization. Aqil M, Sultana Y, Ali A.
26. Mukesh C. Gohel, Rajesh K. Parikh, Stavan A. Nagori, and Dillip G. Jena Fabrication of Modified Release Tablet Formulation of Metoprolol Succinate using Hydroxypropyl Methylcellulose and Xanthan Gum.
27. Optimization of bilayer floating tablet containing metoprolol tartrate as a model drug for gastric retention C. Narendra, M. S. Srinath, and Ganesh Babu.
28. Kannan, K.; Manikandan, M.; Periyasamy, G.; Manavalan, R Design, Development and Evaluation of Metoprolol Succinate and Hydrochlorothiazide Bilayer Tablet Kannan, K.; Manikandan, M.; Periyasamy, G.; Manavalan, *Journal of Pharmaceutical Sciences & Research*, 2012; 4(5): 1827
29. Metoprolol succinate extended release combination tablets James W Hainer and Jennifer Suggested, 4(2): 21-52.