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FORMULATION AND IN- VITRO EVALUATION OF METOPROLOL SUCCINATE MATRIX TABLETS

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ABSTRACT
The objective of present investigation was to prepare and characterize controlled release (CR) matrix tablets of Metoprolol Succinate (MS) using polymers like Hydroxy Propyl Methyl Cellulose (HPMC) K100, Carbopol 934, and Ethocel and also to evaluate different formulation variables like polymers on drug release properties of MS tablets. HPMC is used as hydrophilic polymer, Carbopol and Ethocel are used as rate controlling polymers. MS tablets were prepared by employing the wet granulation technique using 2.5% gelatin concentration as binder to achieve prolonged release of medicaments. The prepared MS tablets were evaluated for hardness, weight variation, FTIR, DSC and drug release kinetics. Release kinetics were evaluated by using USP Type -II dissolution apparatus. DSC and X- RD studies confirmed that MS was not in crystalline state. As MS having less half-life (4-6 hrs.) CR tablets are formulated to enhance half-life of MS tablets and in this research formulation variables are taken from F1 to F17. In vitro drug content release studies explain that high concentration of polymer will retard the drug release such that there is an enhancement of half-life of tablet. Among all the formulations F11 having HPMC 25mg, Ethocel 15mg, and Carbopol 25 mg showed maximum drug release (99.85%) in 24 hrs in controlled manner

INTRODUCTION

Oral administration of drugs is the most predominant route for the delivery of therapeutic agents. Although different route of administration are used for the delivery of drug design, due to flexibility in dosage form and patient compliance oral route is widely preferred [(1)]. Owing to its potential advantages including patient friendly, convenience, ease of administration, accurate dosing, cost effective manufacturing methods, it has been the most favored drug delivery systems in pharmaceutical field [(2)]. So, many scientists had been working on many formulations in the development of dosage forms in regard to the need of the patients. Therefore, a major challenge for the pharmaceutical industry in drug development is to produce safe and efficient drugs.

In this context several dosage forms have developed, of all the dosage forms tablet form have been the major breakthrough in the field of pharmacy as it able to deliver an exact dose of drug along with an easy administration. There are different types of oral dosage forms like capsules, emulsions, suspensions, lozenges, solutions, films, pills, liquids etc… From the above mentioned dosage forms there are problems like administration, inconvenience, method of preparation, stability etc… In this the solid formulation do not require sterile conditions. As above mentioned, tablets are widely used dosage form because of its self- administration, compactness and ease of manufacturing [(3)]. According to Indian pharmacopoeia (IP) pharmaceutical tablets are solid, flat or biconvex dishes, unit dosage form prepared by compressing the drug or mixture of drugs with or without diluents [(4)]. The tablets contains good acceptance for the patients by means of taste masking, convenience, ease of administration and controlling release rate for Effective therapeutic action and also less expensive to manufacture [(5)]. It is the most popular dosage form and majority of total drugs are dispensed in the form of tablets [(6)].

As tablets are extensively used dosage forms, they can formulated into different forms mainly based on their mode of delivery. So drug delivery systems are broadly classified into two types. They are

- Conventional drug delivery systems (CDDS)
- Modified drug delivery systems (MDDS)

❖ CONVENTIONAL DRUG DELIVERY SYSTEMS :

Conventional drug therapy requires periodic doses of therapeutic agents. For most drugs conventional drug delivery is effective, but some drugs are unstable or toxic and have narrow therapeutic window and solubility [(7)]. Conventional dosage forms are rapidly absorbed, with the ascending and descending portions of the concentrations versus time curve [(8)].

Some limitations of CDDS are given below.

- ✓ The dosing pattern in conventional dosage form results in constantly changing, leading to marked side effects in some cases.
- ✓ Poor patient compliance, increased chances of missing the dose with short half-life leads to frequent administration is necessary.

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

- ✓ A typical peak-valley plasma concentration time profile is obtained which makes steady state is difficult. In this immediate release systems are placed.

  Immediate release drug delivery systems: These are dosage forms which are designed to disintegrate and release their medication without any special rate controlling features like coatings. These delivery systems can release the drug within 3 to 5 minutes.

- ❖ **MODIFIED DRUG DELIVERY SYSTEMS:**

  Some dosage forms can be designed to modify the release of a drug over a given period of time after the administration to reach a specific target in the body. These modifications are done in order to improve therapeutic outcome of the drug, increase stability, safety and efficacy of the drug.

- ✓ MDDS are classified into two types based on release rate of the drug. They are

a. Delayed release
b. Extended release

- ▪ Sustained release
- ▪ Controlled release

- ➢ Dissolution : 1. Matrix
  2. Encapsulation
- ➢ Diffusion : 1. Matrix
  2. Reservoir
- ➢ Combination of both dissolution and diffusion systems
- ➢ Osmotic pressure release controlled systems

- ➢ **NEED OF STUDY:**

  Hypertension is the leading cause of death across the world. Apart from heart it also affects other organs in body which cause multi-level damage. As it is the most occurring disease in the present scenario and the people affecting by it are most we selected the drug which works efficiently against it.

  Metoprolol succinate is a cardio selective beta blocker used in treating hypertension. It is available commercially in 25mg, 50 mg strength as immediate release tablets with 50% bioavailability. Frequent administration and less bioavailability leads to plasma concentration fluctuations and causes less patients compliance. Hence, this problem can be solved by formulating this drug into controlled release matrix formulation which maintain concentration of drug in blood for longer time and the strength is 100mg. We aim at increasing the bioavailability about 100%.

2. AIM AND OBJECTIVE

AIM:

To formulate and evaluate the Metoprolol succinate controlled release matrix tablets using Box-Behnken by design of expert software.

OBJECTIVES:

- ❖ Calibration of the Metoprolol Succinate using UV Visible spectrophotometer.
- ❖ Assembling the data of different formulations using Box-Behnken design.
- ❖ Preparation of tablets using the data collected from the design.
- ❖ Evaluation of the physical parameters of the prepared tablets and the tests are given below:
- ✓ FTIR studies
- ✓ X-RD Analysis
- ✓ DSC studies
- ✓ Thickness and diameter
- ✓ Weight variation
- ✓ Hardness test
- ✓ Friability test
- ✓ Content uniformity

1. 3. LITERATURE REVIEW

The literature survey for Metoprolol succinate was carried by several authors and some they were given below:

Sandra Klein et al, 2018. Formulated extended release hydrophilic matrix tablets, using high viscosity grade of Hypromellose as a rate limiting polymer. This formulation showed an undesirable initial burst release followed by controlled drug release. Application of barrier membrane coating of ethyl cellulose with a pore former resulted in the elimination of burst release. When it is subjected to dissolution studies, the BM coated formulation show robust drug release without an initial burst in all test scenarios. Thus BM coated matrix formulations represents a very promising approach for obtaining a highly controlled and robust drug release from oral ER formulations.

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

J Souri et al, 2017. used Captopril, ethyl cellulose N100 hydroxy propyl methyl celluloseK15M as polymers .The results show that the concentration of HPMC K15M increases the spreading coefficient of polymer over mucous and mucous over polymer are more positive, thus increasing the contact between the matrix tablets with mucous layer. Therefore this formulation has the greatest potential mucoadhesion capability.

Alessia lazzari et al, 2017.The vulnerability of control release formulations when congested with alcohol represents a current major concern of regulatory agencies. Dose dumping might occur when drugs and excipient exhibit higher solubility in ethanol solutions compared to water. In this study can than gum was chosen as rate controlling polymer for the development of alcohol resistant matrix formulations and theophylline as model drug .Two polymer particle sizes and concentrations were used to assess their influence on the invitro drug release from directly compressed tablets and mini tablets in 0% and 40% ethanol for 2 hours. By decreasing the polymer concentration a risk of alcohol induced dose dumping was recognised however only when larger polymer particles were used. Nevertheless finer polymer particles used at low concentration left the formation of more coherent and less porous gel layer and alcohol resistance could be tailored in regard to both matrix tablets and mini tablets.

Pavani et al, 2017.This study involved to develop sustained release formulation of tramadol hydrochloride to maintain constant therapeutic levels of drug for over 24 hours. By using different ratios of synthetic polymers like ethyl cellulose, Eudragrit RL100, natural polymers like moringa gum and tamarind gum were employed as a polymer all the formulations were passed various physicochemical evaluation parameters and they were found to be within limits. Whereas from the dissolution studies it was evident that the formulations showed better and undesired drug release pattern that is 100.6% in 24hrs. It contains the tamarind gum1:2 ratio as sustained release material. It followed Higuchi release kinetics mechanism.

Sa kiko fukui et al, 2016.The purpose of this study was to develop an extended release (ER)matrix tablets that shows robust dissolution properties able to account for the variability of pH and mechanical stress in the GIT using a combination of enteric polymer and hydrophilic polymer. Hypromellose Acetate succinate (HPMCAS) and Hydroxy Propyl Cellulose (HPC) were selected as ER polymers for the ER matrix tablet. Dissolution properties of HPMCAS and HPC ER matrix tablets were evaluated and were not affected by the pH of the test medium or paddle rotating speed. The plasma concentration time profile simulated was similar to that of reference product. These results suggest that the combination of HPMCAS and HPC shows a robust dissolution profile against pH and paddles rotating speed and indicates the appropriate extended release profile in humans.

A Satya raj et.al, 2014. To develop control release tablets of Metoprolol succinate using natural polymer, guar gum and synthetic polymer, carbopol as a rate controlling polymer. It was also desired to study the effect of polymer concentration. Metoprolol succinate is a beta one selective adrenergic receptor blocking agent used in the management of hypertension angina pectoris, cardiac arrhythmias, heart failure, and in the prophylactic treatment of the migraine. The half-life of drug is relatively short approximately 4-6hrs and in normal course of therapy drug administration is required every 4-6hrs thus warrants the use of controlled release formulation for prolonged action and to improve patient compliance in the present investigation natural polymer, guar gum and synthetic polymer carbopol have been selected as matrix forming materials for the drug. The formulations are made by employing the conventional wet granulation method to achieve prolonged release of medicaments.

- **CH Chandana et al,** 2014. Metoprolol succinate matrix tablets were prepared by direct compression method using different polymers like HPMC, K1OOM, HPMC K15M, Sodium CMC, pectin. All the formulation is subjected to invitro dissolution studies.

- **Singvi gautam et al,** 2012. They designed and evaluated the release matrix type of Metoprolol succinate using HPMC, Eudragits a matrix forming agents. HPMC was used to form firm gel with Eudragit polymer. The drug release mechanism was predominantly found to be Non-Fickian diffusion controlled.

- **Hema Ravi Shankar et al,** 2012. A modulated release ,multiunit oral drug delivery technology using a system based on ionic interactions of anions of salts with quaternary ammonium ions of the ammonio methacrylate polymer is described .The Eudragrit NE a salt core which was further coated Eudragrit RS. A Protype formulation of Metoprolol succinate using this technology was developed and the drug release from the formulation was adjusted to have a release profile which would match the circadian rhythm.

- **Jamal ahmad et al,** 2011.In the present investigation lomoxicam bilayer matrix tablets were prepared by using HPMC, CMC and sodium alginate as release retardants. Drug and polymer interaction study were done and results revealed that there was no interaction between drug and polymers. Lamoxicam bilayer tablets contained two layers, one is for

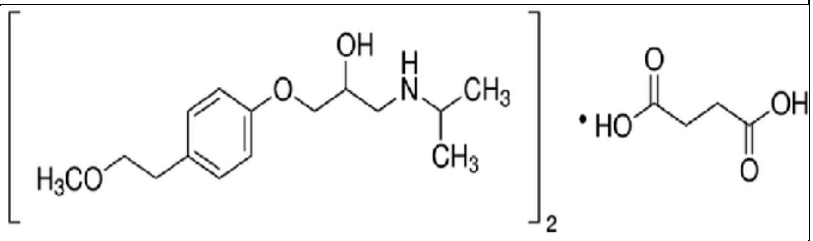
ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

immediate release and another for sustained release of lomoxicam. The formulations were evaluated and the parameters within acceptable pharmaceutical specifications. The formulation F-5prepared by using HPMC K15 80% was shown by drug release of 98.68 at the end of 24 hrs. The formulation F-10 prepared by using sodium alginate 80% shown the drug release of 98.79% at the end of 12hrs. The formulation F-15 prepared by using CMC80%shown the drug release of 98.98at the end of 9hrs. From these results it clearly indicates that it was possible to sustain the lomoxicam release photo 24hrs by using HPMCK15 80% whereas polymers CNC and sodium alginate could not able to sustain the release up to 24 hours.

4. **METOPROLOL SUCCINATE PROFILE**

4.1 PHYSICO CHEMICAL PROPERTIES:

Table 4.1 Physico -Chemical Properties of Metoprolol Succinate

S.NO	PARAMETER	DESCRIPTION
1	State	Crystalline
2	Colour	White
3	Molecular Formula	[(C15H25NO3)².C4H6O4]
4	Chemical Name	(±) 1-(Isopropyl amino)-3-[P-(2- Methoxyethyl) propoxy]-2-propronol succinate (2:1) salt.
5	Molecular Weight	652.81
6	Solubility	Freely soluble in methanol, sparingly solubility in ethanol, insoluble in ethyl acetate, acetone, di ethyl ether and heptane.
7	Route of administration	Oral route
8	Structure	
9.	Dose	50,100,200 mg

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

4.2 PHARMACOKINETIC PROFILE:

Table 4.2 Pharmacokinetic Parameters of Metoprolol Succinate.

S.NO	PARAMETER	VALUES
1.	Absorption	In intestine.
2.	distribution	Approx. 10%
3.	Metabolism	Metoprolol is metabolized by cytochrome p450 in liver.
4.	Excretion	By kidney through urine
5.	Half life	3-7 hrs
6.	Bioavailability	Approx. 20-30 % for controlled release tablets.

4.3 PHARMACODYNAMIC PARAMETERS:

Table 4.3 Pharmacodynamic Parameters Of Metoprolol Succinate.

S.NO	PARAMETER	VALUES
1.	Total body clearance	Between 43.2 to 92.4
2.	Metabolism	Metoprolol is a racemic mixture and is primarily metabolized by CYP2D6 and small percentage by CYP3A4.
3.	Receptor	β_1 Adrenergic receptor.
4.	Contra indications	• Age shows little influence on Metoprolol • In pregnancy and lactating women
5.	Interactions	• Metoprolol with Alcohol shows additive effects in lowering blood pressure. • Metoprolol with multi-vitamin and minerals may decrease the effect of metoprolol. • Metoprolol should be avoided in diseased conditions like Brady arrhythmia, cardiogenic shock, CHF, Diabetes, liver diseases , glaucoma etc

5. MATERIALS AND METHODS

S.NO.	MATERIALS	SUPPLIERS
1.	Metoprolol	Thermo fisher scientific Noida
2.	HPMC K100	Research lab fine chem. Ind
3.	Ethocel E1415	Otto kemi
4.	Carbopol 934	LOBA CHEMIE PVT.LTD
5.	Mg.sterate	Research lab fine chem. Ind
6.	MCC	LOBA CHEMIE PVT. LTD
7.	Talc	LOBA CHEMIE PVT. LTD
8.	Gelatin	Research lab fine chem. Ind

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

9.	Sodium Hydroxide	LOBA CHEMIE PVT. LTD
10.	KH_2PO_4,Ethanol	LOBA CHEMIE PVT. LTD

Table5.1 Materials that are used in the study

5.2 Table: Equipments that are used in study

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S.NO	NAME OF THE EQUIPMENT	MANUFACTURER
1.	Electron balance	WENSAR
2.	Electron balance (mg)	SHIMADZU
3.	Digital pH- meter	Eli co LT120
4.	Rotary machine	General ph.machinery.co
5.	Dissolution apparatus	Lab India DS8000
6.	U.V Spectro photometer	Lab India2000U
7.	Friabilator	SECOR INDIA
8.	Pfizer	Dolphin
9.	Monsanto	SECOR INDIA

5.2 METHODS:

5.2.1 PREPARATION OF BUFFER:

The buffer solution was prepared as per the procedure given in I.P. 0.88gm of sodium hydroxide was accurately measured and was transfer into 1000ml volumetric flask. To this add 5.22gm of potassium di hydrogen orthophosphate. Distilled water was added slowly and mixed well and made the volume up to 1000ml. Measure the pH the of buffer solution in pH meter.

5.2.2 PREPARATION OF STOCK SOLUTION:

Accurately weigh the 10mg of Metoprolol succinate in 10ml volumetric flask. It was dissolved in 2-4ml of ethanol and made up to 10ml with p^H 6.8 buffer solution. For determination of dissolution samples, a series of dilution containing 2, 4, 6, 8, 10 µg/ml were made by the stock solution and measure the absorbance at 223nm against blank.

5.2.3 PREPARATION OF TABLETS USING WET GRANULATION METHOD [16,17]:

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

Ingredients (mg)	**F 1**	**F 2**	**F 3**	**F 4**	**F 5**	**F 6**	**F 7**	**F 8**	**F 9**	**F 10**	**F 11**	**F 12**	**F 13**	**F 14**	**F 15**
METOPROLOL	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
ETHOCEL	15	5	5	25	25	15	5	25	15	5	15	15	25	15	15
HPMC K100	5	15	5	15	25	15	15	15	25	25	25	5	5	15	15
CARBOPOL 934	25	25	15	5	15	15	5	25	5	15	25	5	15	15	15
Mg. STERATE	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
TALC	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
MCC	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5

The drug and polymers like carbopol, HPMC, ethocel were accurately weighed, triturated and made into a fine powder using motor and pestle. It is made into a damp mass using gelatin 2.5% as a binder. Granules were prepared by passing the mass through the sieve no.10 and the granules were dried in hot air oven at 40^0C until the granules become dried. Now pass these dried granules through sieveno.22/44 to the granules add magnesium stearate and Talc for lubrication and glidant. Adjust the final weight of the tablet using MCC. Now the granules were compressed by using rotary punching machine using a punch of 8mm.

5.3 EVALUATION OF PHYSICAL PROPERTIES OF MATRIX TABLETS

- FTIR
- DIFFERENTIAL SCANNING CALORIMETRY
- X RAY DIFFRACTION STUDIES
- THICKNESS AND DIAMETER
- WEIGHT VARIATION TEST
- HARDNESS TEST
- FRIABILITY TEST
- CONTENT UNIFORMITY
- DISSOLUTION STUDIES OF MATRIX TABLET CONTAINING METOPROLOL SUCCINATE
- RELEASE KINETICS STUDY
- ZERO ORDER KINETIC MODEL
- FIRST ORDER KINETIC MODEL
- HIGUCHI MATRIX MODEL
- KORSMEYER PEPPAS MODEL

Table 5.4 Various Formulations of Metoprolol Succinate.

6. RESULTS AND DISCUSSION

DETERMINATION OF λ_{max} OF METOPROLOL SUCCINATE:

Initially, 10 mg of drug was dissolved in little amount of water but drug did not get dissolved in it. Hence ethanol was used instead of water to get the drug dissolve. This dilution was scanned in UV and peaks were observed. The absorption maximum of Metoprolol succinate was found to be 223nm and this wave length was selected and utilized for further studies.

PREPARATION OF MS MATRIX TABLETS:

Matrix tablets were prepared by wet granulation technique using Carbopol, HPMC, and Ethocel as polymers. The dose of MS was 100mg and the final weight of the tablet was equivalent to 200Mg.

FTIR ANALYSIS:

The MS showed characteristic peaks at cm^{-1}. These characteristic peaks of were all retained in the formulations. These results were given in Table and indicate that there is no interaction between MS& excipients in MUPS. The spectra of MS and MS MUPS were shown in Fig

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

Table 6.1 FTIR Spectral Data of Metoprolol succinate

Functional group	Vibration	Frequency range(cm^{-1})	Frequency Obtained for MS(cm^{-1})
O-H	Stretching	970-1250	1156
N-H	Stretching	3300-3400	3310
CH2CH2&CH	Stretching	2960-2850	2960

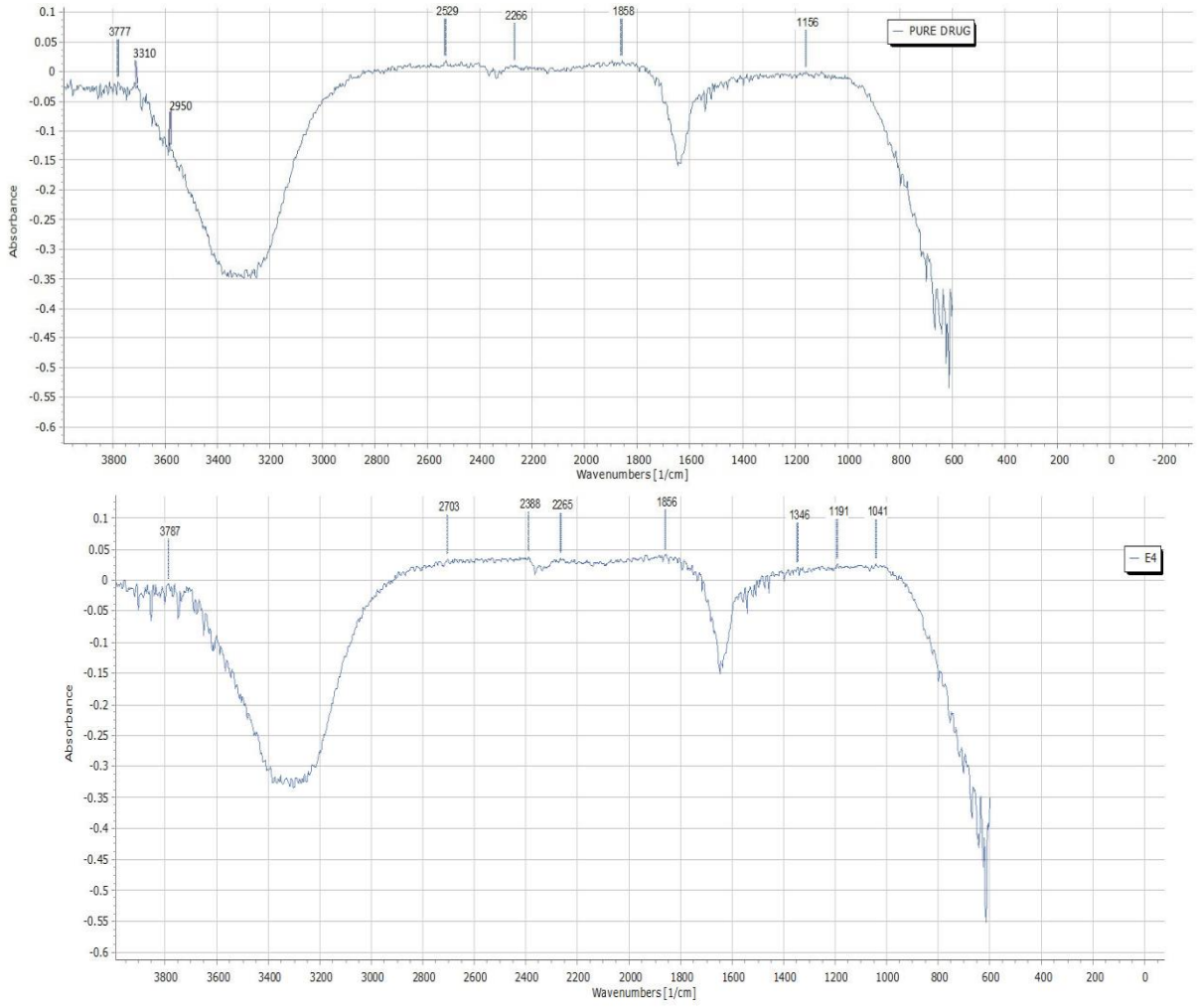

Fig FT-IR Spectra of MS

DRUG CONTENT:

Matrix tablets of Metoprolol succinate were prepared by wet granulation technique. Based on USP drug content of each tablet should be in the range of 85-115% of the theoretical label claim. All the formulations showed good uniformity in drug content and the percent of drug content was 92.55 to 99.85. The values of the content uniformity varies for different formulations depending upon the amount of polymers used in those formulations. The content uniformity for formulation F11 is found to be maximum i.e.., 99.85 when compared to other formulations because as

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

it contains the maximum amount of the polymers. The difference in drug content may be due to the difference in the polymer concentration. The formulations F1, F2 and F5 have shown the drug content in the range of 92.55 to 92.80. This may be due to the polymer concentration we used in the formulations. The formulation F3, F4, F6, F10 and F13has shown the drug content in the range of 95.11 to 96.77.

HARDNESS:

Matrix tablets of Metoprolol succinate were prepared by wet granulation method and the hardness of tablets belonging to different formulations were evaluated. The hardness of the tablets ranges from 1.8 to 3 kg/cm^2. The F1, F2 and F11 formulations have carbopol in more amount. Hence, their hardness ranges from 1.8 to 2kg/cm^2. The hardness values for F3, F5, F6, F10 and F13 ranges from 2.0 t0 2.4kg/cm^2. This may be due to presence of lesser amount of carbopol present in these formulations.

The hardness values for remaining formulations i.e.., F4,F7,F8,F9 and F12 ranges from 2.4 t0 3 kg/cm$^{2.}$ This also may be due to lesser amount of polymer used i.e.., 5mg.

From the above statements we can say that as the concentration of the polymer increases their hardness also increases and vice-versa.

The hardness values for formulations F1 to F13 were tabulated in the table 6.2.

Table Standard Deviation values of Hardness

S.No	Trail1	Trail2	Trail 3	AVG ± SD
1	1.8	1.7	1.8	1.76±0.05
2	2	2.1	2.2	2.1±0.1
3	2.2	1.9	2.1	2.06±0.15
4	3	2.9	3.1	3±0.1
5	2	2.2	1.9	2.03±0.15
6	1.8	1.9	2.1	1.93±0.15
7	2.4	2.3	2.2	2.3±0.1
8	1.9	2	2	1.96±0.05
9	2.4	2.1	2.3	2.26±0.15
10	1.8	1.7	1.9	1.8±0.10
11	1.8	1.9	1.2	1.63±0.37
12	2.5	2.4	2.3	2.4±0.10
13	2	1.9	2.2	2.03±0.15

WEIGHT VARIATION:

Matrix tablets of Metoprolol succinate were prepared by wet granulation method and are subjected to weight variation test. According to I.P the weight variation limits for tablets weighing more than 80mg or less than 250mg ± 7.5% deviation is acceptable. The tablets of formulations from F1 to F13 have shown weight variation below ±1.46% and are found to be within the IP limits. Thus, we can say that all the formulations met the requirement. The standard deviation values for formulation F1 to F13 were tabulated in the table 6.3.

FRIABILITY:

The matrix tablets of Metoprolol succinate were prepared by wet granulation method. According to IP the friability values of the tablets should be below 1%.

The given all formulations have shown the friability values less than or equal to 1% and has met the given requirement.

INVITRO DRUG DISSOLUTION:

The dissolution studies were carried out in USP type-II apparatus at 50 rpm using pH 6.8 phosphate buffer and the temperature maintained was 37.5 ^{0}c.The aliquots were withdrawn at certain time intervals and values of different formulations were tabulated in the tables given below and graphs were plotted:

The cumulative percent of drug released from the F1 (5% carbopol) 50% is for 6hrs, which is 1.2 times greater than the drug release from F2 (8% HPMC), may be due to the high viscous nature of the carbopol retarted the MS release from the formulation. The complete release of MS from F1 is found to be with in 8hrs whereas the complete release of MS from F2 is found to be within 6hrs indicating that carbopol controls the release of MS compared to MS.

The cumulative percent of drug release from F1 formulation 50% is for 4 hours (5% HPMC) but it takes 6 hours for F2 formulation to show 50% of drug release(15% HPMC).This may be due to the high concentration of HPMC in F2

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

formulation which retards the release of drug from formulation. The maximum release takes place within 12 hours in F1 formulation but in F2 formulation it takes more than 12 hours.

The cumulative percent of drug release from F2 formulation 50% is for 6 hours(25% carbopol) but it takes only 5 hours to release 50% of drug release in F3 formulation (15% carbopol) which is 1 time greater than F1. This may be due to the high concentration of carbopol in F2 formulation which retards the release of Metoprolol succinate.

The cumulative percent of drug release from F3 formulation 50% is for 5 hrs time interval (15% carbopol) which is 1 time greater than the drug release from F4 formulation (15% HPMC). This may be due to the high viscous nature of carbopol from F3 formulation.

The cumulative percent of drug release from F4 formulation 50% is for 4 hours (5% carbopol) which is 1 time lesser than F5 formulation (15% carbopol, 25% HPMC).This may be due to the high concentration of carbopol in F5 formulation.

The cumulative percent of drug release from F5 formulation 50% is for 5 hours which is same as that of F6 formulation. This may be because of the equal concentration of carbopol in both the formulations.The cumulative percent of drug release from F6 formulation 50% is for 5 hours' time interval which is one time greater than that of F7 formulation (5% carbopol). This may be due to the equal concentration of all the polymers in F6 formulation.The cumulative percent of drug release from F7 formulation 50% is for 6 hours' time interval (5% ethocel) which is one time lesser than that of F8 formulation (25% ethocel). This may be due to the higher concentration of ethocel in F8 formulation.

The cumulative percent of drug release from F8 formulation 50% is for 5 hours' time interval which is same as that of the F9 formulation. This may be due to the equivalent concentrations of the polymers in those formulations.

The cumulative percent of drug release from F9 formulation 50% is for 5 hours' time interval(5% carbopol) which is one time greater than F10 formulation(15% carbopol). This may be due to the higher concentration of carbopol in F10.

The cumulative percent of drug release from F10 formulation 50% is for 4 hours which is 2 times lesser than that of F11 (25% carbopol).This may be due to the higher viscous nature of the carbopol in F11.

The cumulative percent of drug release from F11 formulation 50% is for 6 hours' time interval (25%carbopol,25%HPMC) which is 1 time greater than that of F12(5% carbopol and HPMC). This may be due to the higher concentration of carbopol and HPMC in F11 formulation.

The cumulative percent of drug release from F12 formulation 50% is for 5 hours' time interval(HPMC, Carbopol 5%,ethocel 15%) which is 1 time greater than F13(HPMC 5%). This is due to the more amount of ethocel.

F1 Formulation:

Table %Drug dissolved values of [F1] and their Standard Deviation values.

	% Drug Dissolved			
Time(hr)	**T1**	**T2**	**T3**	**AVG ± STD**
0	0	0	0	0
0.5	27.2	28.62	27.44	27.75±0.76
1	33.3	32.03	32.25	32.52± 0.67
1.5	36.41	36.23	36.78	36.47± 0.28
2	39.15	40.33	37.24	38.90± 1.55
3	47.2	45.95	46.28	46.47± 0.65
4	49.36	51.75	49.37	50.16±1.37
5	54.25	55.21	52.46	53.97±1.39
6	56.5	57.75	55.55	56.6±1.10
7	59.98	60.55	58.64	59.72±0.98
8	62.93	64.49	61.73	63.05±1.38
9	68.91	69.14	64.82	67.62±2.43

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

10	76.26	75.63	67.91	73.26±4.64
11	86.12	83.86	84.9	84.96±1.13

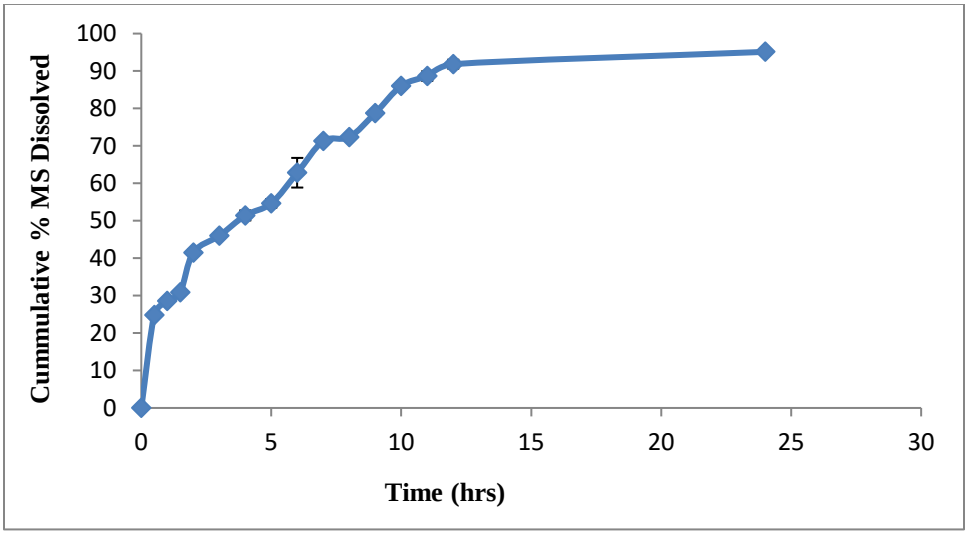

Fig 6.10.1, Invitro Dissolution Profile of Ms in pH 6.8 Buffer [F1]

The formulation F14, 15, 16 and 17 have same amount of polymers as that of F6. Hence, they are expected to give same results as that of F6 formulation. During the initial stages of development of the tablets the polymer used is excess hence the release of the drug from the matrix has taken more time and it has not shown the maximum drug release. Based on this we decreased the concentrations of the polymers. The polymers used include HPMC, ethocel and carbopol. The usage of carbopol results in formation of lump with the usage of 5% gelatin. Hence, the concentration of gelatin was reduced to 2%.Less than 1 ml of the gelatin was consumed in wet granulation. The hardness of the tablets were reduced from 4 kg/cm^2 to 1.8 kg/cm^2 because of the formation of matrix within the tablet in order to release the drug from the matrix in required time.

30mg of the drug is placed separately during punching over the granules in order to attain the 30% of drug release within 30mins of time interval which shows faster onset of action. The dissolution studies were performed for 24hrs of time. Different formulations had shown different % of drug release within 24hrs of time.

The F1 formulation shows the drug release up to 92.99% within in 24 hour time interval. The F2 formulation shows the drug release up to 92.55% within in 24 hour time interval. The F3 formulation shows the drug release up to 95.87% within in 24 hour's time interval. The F4 formulation shows the drug release up to 95.11% within in 24 hours' time interval. The F5 formulation shows the drug release up to 92.80% within in 24 hour's time interval. The F6 formulation shows the drug release up to 95.84% within 24 hours' time interval.F14,F15,F16 and F17 have same amount of polymer concentrations like that of F6 hence, they show the same amount of drug release as that of F6 formulation. The F7 formulation shows the drug release up to 98.82% within in 24 hours' time interval. The F8 formulation shows the drug release up to 98.74% within in 24 hour time interval. The F9 formulation shows that drug release up to 98.02% in 24 hour time interval. The F10, F11, F12 and F13 formulations shows 96.77, 99.89, 98.5 and 96.27% of drug release in 24 hours' time interval. The maximum amount of the drug release is shown in formulation 11. The percentage of the drug content is compared by plotting the different comparative graphs. Comparative graphs were drawn by keeping the concentrations of the polymer constant.

3D GRAPHS

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3d graphs for all the Polymers in all the concentrations i..e, ethocel-5%,15%,25%; HPMC k100-5%,15%,25%;carbopol-5%,15%,25% for $T_{50\%}$ are as follows

8.1 3D PLOTS FOR $t_{50\%}$

- **FACTOR A (ETHOCEL)**
- **FACTOR B (HPMC)**
- **FACTOR C (CARBOPOL)**

8.2 3D PLOTS FOR $t_{90\%}$

- **FACTOR A (ETHOCEL**
- **FACTOR B (HPMC)**
- **FACTOR C (CARBOPOL)**

8.3 3D PLOT FOR T_{max}

8.4 3D PLOTS FOR $\%DE_{30}$

- **FACTOR A (ETHOCEL)**
- **FACTOR B (HPMC)**
- **FACTOR C (CARBOPOL)**

ANOVA VALUES FOR 3D PLOTS

ANOVA values are considered if the runs or models give the probability value less than 0.05 are significant. When compared to all the responses $\%DE_{30}$ and t_{90} responses are considered as significant than t_{max} and t_{50}. ANOVA values of the different responses are given below.

7.SUMMARY AND CONCLUSION

Oral drug administration has been the predominant route for drug delivery. It is known to be the most popular route of drug administration. A controlled release drug delivery system delivers the drug locally or systemically at a predetermined rate for a specified period of time. The goal of such systems is to provide desirable delivery profiles that can achieve therapeutic plasma levels. We have used a software named design expert to perform the design of experiments.

Design expert, a software was used in our experiment for performing DOE that is design of experiments. This design expert is a statistical software package from stat-ease in which is specifically dedicated for performing DOE.

Generally DOE done manually is a hit and trail method which may cause wastage of lot of chemicals and it is time consuming. It may also cause errors. While the usage of this software reduces the wastage of time, chemicals and overall cost of the research work. Drug release is dependent on polymer properties and hence these polymers were used in order to achieve the desired matrix system. The polymers used include HPMC, ethocel and carbopol. The release of drug from the matrix depends upon the concentration of the polymers used. Here controlled release matrix tablets of metoprolol succinate were formulated and they were evaluated. The evaluations include content uniformity, swelling index, thickness and diameter, friability and hardness. The calibration graph was plotted and the lamda was determined. The lamda max was found to be 223nm. The dissolution studies were performed for different formulations from F1 to F13 and the graphs were plotted.

CONCLUSION: Finally we concluded that controlled release matrix tablets of Metoprolol Succinate were successfully formulated and evaluated. From the values of % drug release formulation F11 shows drug release of 99.85% due to the higher concertation of polymers like Carbopol and HPMC that retard the release rate. F11 formulation shows the half life of 6hrs and maximum release in 24 hrs which is due to maximum polymer concentration when compared to remaining formulation.

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