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Research Article

Formulation and Evaluation of Controlled Release Tablets of Metoprolol Succinate by - Osmotic Drug Delivery

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ABSTRACT

Osmotically controlled drug delivery systems utilize the principle of osmotic pressure for the controlled delivery of active agents. The release rate of the drug from these systems is independent of the physiological factors of the gastrointestinal tract to a large extent. Metaprolol succinate β-receptor blocking agent was selected as a model drug to be formulated into osmotic drug delivery system. Elementary osmotic pump core tablets for Metaprolol succinate non- aqueous wet granulation were prepared by using osmogens like KCl. The coated tablets were drilled to different orifice sizes by using mechanical microdrill by mechanical means using softclix - modified sharp needle. The drilled orifice sizes on coated tablets were evaluated by using scanning ocular micrometer. It was observed that with an increase in osmogen content and pore size, rate of drug release was found to be increasing. The rate of drug release was found to be decreased with an increase in the membrane thickness. Based on different experimental trials, the optimized formulation was selected with respective to osmogen concentration, membrane thickness and orifice size that are following zero-order controlled release from the elementary osmotic pump tablets. The final selected elementary osmotic pump tablets have shown comparable dissolution profile with respective to marketed formulation.

Keywords: Metoprolol succinate, KCL, controlled release

INTRODUCTION

Controlled release [1] technology has rapidly emerged over the past few decades as a new field offering approaches to the delivery of drugs into systemic circulation at predetermined rate. Controlled release formulations [2] can achieve optional therapeutic responses, prolonged efficacy as well as decrease toxicity duo to achieving predictable and reproducibility release rate of drugs for extended period of time.

CR delivery systems provide desired concentration of drug at the absorption site permitting maintenance of plasma concentration within the therapeutic range and reducing dosing frequency. CR products provide significant benefits over immediate release formulations including greater effectiveness in the treatment of chronic conditions, reduced side effects, and greater patient convenience due to a simplified dosing schedule.

Osmosis[3] can be defined as the passage of solvent molecules into a solution (containing both solute and solvent molecules) thought SPM or passage of solvent molecules usually water takes place from the SPM from a region of lower concentration to higher concentration.

Osmosis pressure [4] can be defined as the pressure exerted as a result of osmosis or the pressure with which the solvent molecules cross

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from the semipermeable membrane or the required to stop the flow of solvent molecules from crossing the SPM is known as osmosis pressure.

The phenomenon of confining a solution to a membrane, permeable only to the solvent molecules, is known as osmosis and the membrane that allows only the solvent molecules to pass through, is known as semipermeable membrane[5] (SPM). Therefore osmosis can be defined as the passage of solvent molecules into a solution (containing both solute and solvent molecules) thought SPM or passage of solvent molecules usually water takes place from the SPM from a region of lower concentration to higher concentration.

Elementary osmotic pump[6,7]

In 1975, the major leap in osmotic delivery occurred as the elementary osmotic pump for oral delivery of drugs was introduced. The pump consists of an osmotic core containing the drug, surrounded by a semipermeable membrane with a delivery orifice. When this pump is exposed to water, the core imbibes water osmotically at a controlled rate, determined by the membrane permeability to water and by the osmotic pressure of the core formulation. As the membrane is non-expandable, the increase in volume caused by the imbibition of water leads to the development of hydrostatic pressure inside the tablet. This pressure is relieved by the flow of saturated solution out of the device through the delivery orifice. This process continues at a constant rate until the entire solid agent inside the tablet has been dissolved and only a solution filled coating membrane is left. This residual dissolved agent continues to be delivered at a declining rate until the osmotic pressure inside and outside the tablet are equal. Normally, the Elementary osmotic pump delivers 60-80% of its contents at a constant rate, and there is a short lag time of 30-60 min as the system hydrates before zero order delivery from the Elementary osmotic pump is obtained.

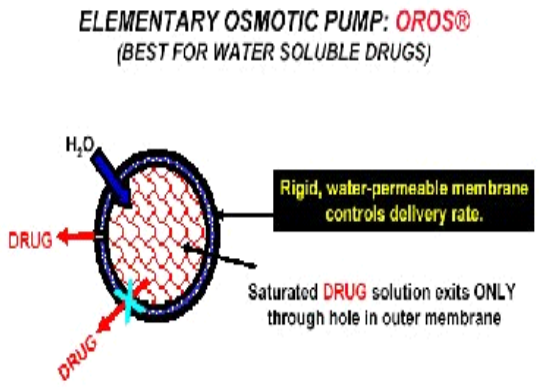

Fig 1: Schematic diagram of Elementary osmotic pump

DELIVERY ORIFICE [8]

To achieve an optimal zero order delivery profile, the cross sectional area of the orifice must be smaller than a maximum size to minimize drug delivery by diffusion through the orifice. Furthermore, the area must be sufficiently large, above a minimum size to minimize hydrostatic pressure build up in the system. The typical orifice size in osmotic pumps ranges from 600µ to 1 mm.

Metoprolol succinate[8] is a cardioselective β1-adrenergic blocking agent used for acute myocardial infarction (MI), heart failure, angina pectoris and mild to moderate hypertension. It may also be used for supraventricular and tachyarrhythmias and prophylaxis for migraine headaches.

Mechanism of action:

Metoprolol competes with adrenergic neurotransmitters such as catecholamines for binding at beta(1)-adrenergic receptors in the heart. Beta(1)-receptor blockade results in a decrease in heart rate, cardiac output, and blood pressure.

Absorption is rapid and complete, 50%.

Biological half life is 3 - 7 hours and its therapeutic use in chronic respiratory diseases

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necessitates its formulation in to controlled release dosage forms.

MATERIALS AND METHODS

Materials:

Metoprolol succinate was recieved as a gift sample from Dr.Reddy's laboratories ltd, kcl, Microcrystalline cellulose 101 grade, Magnesium stearate, cellulose acetate, polyvinyl pyrrrolidone K30, triethyl citrate was recieved from Drugs India Ltd.

Equipment:

Tablet compression machine 8 stn (Rimek), tablet compression machine 10 stn (pacific),gans coater machine (Gansons), fluid bed dryer (Ritsch), rapid mixer granulator (Kevin), Friabilator tester (Electrolab), Hardness tester(Dr.schleuinger phermotron), Tablet disintegration tester (Eletrolab), Halogen moisture Analysis (mettlertoledo), Tap density tester (Electrolab), Octagonal blender (Gansons)

Methodology:

Steps involved in manufacturing of tablets:

- Dispense the active pharmaceutical ingredients and excipients as per batch requirement.
- Metoprololsuccinate, Microcrystalline Cellulose were sifted through # 30 sieves.
- Potassium Chloride was passed through # 100 sieve
- Metoprolol succinate, Microcrystalline Cellulose,Potassium Chloride was mixed in Rapid mixture granulator for10 mins.
- Prepared 4% PVP-k-30 with isopropyl alcohol, used as binding agent.
- Binder solution was added at a flow rate of 6ml/min to the premixed contents of step IV in the RMG to get a coherent wet mass.
- This wet mass was kneaded for 2-3 min to get wet granules.
- The wet Granules were passed through # 18 sieve and then dried in a fluid bed dryer at 30°c for 20mins at an airflow of 20 cfm (cubic foot per mint)
- The moisture content of the granules was determined by the moisture balance analyzer (LOD).
- The granules were loaded into the blend and mixed for 10min at 20 rpm
- Added the required quantity of magnesium stearate (sifted through # 50 sieve) and blend for another 5 min at 20 rpm.
- Compressed tablets equivalent to make 525mg metoprolol succinate using 10.5 mm round standard concave punch.
- The formulation was prepared for 600 tablets batch size.

Table 1:Formulation of metoprolol succinate core tablets 525 mg

Core composition							
INGREDIENTS	**Drug compartment composition, mg/core tablet (variable)**						
Batch no:	**Fo 1**	**Fo 2**	**Fo 3**	**Fo 4**	**Fo 5**	**Fo 6**	**Fo 7**
Ratio(M S :osmotic)	1:00	1:0.25	1:05	1:0.75	1:0.875	1:01	1:1.25
Metoprolol succinate	200	200	200	200	200	200	200
Potassium Chloride #100	0	50	100	150	175	200	250
Microcrystalline Cellulose-112	302.5	252.5	202.5	152.5	127.5	102.5	52.5
Polyvinylpyrrolidone-k-30	20	20	20	20	20	20	20
Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Average weight	525	525	525	525	525	525	525

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Evaluation of developed core formulation:

Granules were evaluated for various tests like Bulk density, Tap density, Carr's compressibility index, Hausner Ratio, loss on drying. Tap density, Bulk density, Carr's compressibility index, Hausner Ratio was determined by tap density tester and loss on drying was determined by Halogen moisture Analysis

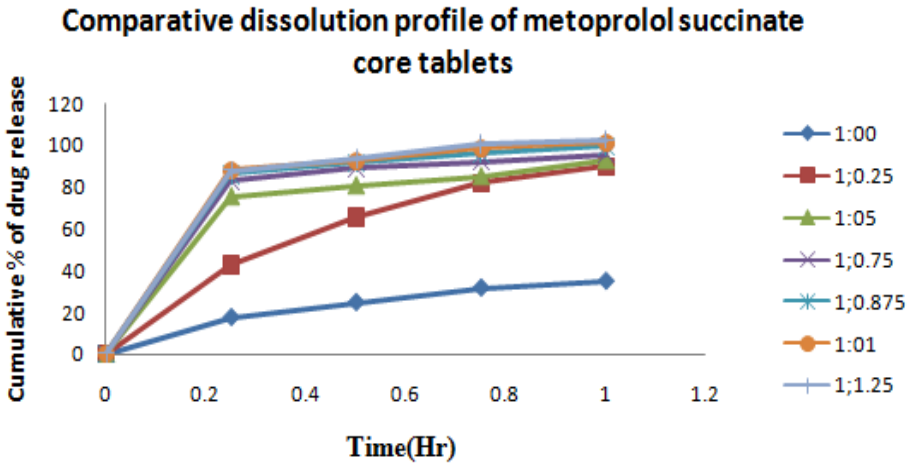
Table 2: EVALUATION OF THE PHARMACEUTICAL POWDERS AND TABLETS

physical parameter	Fo 1	Fo 2	Fo 3	Fo 4	Fo 5	Fo 6	Fo 7
Ratio(M S :osmotic)	1:00	1;0.25	1:05	1:0.75	1:0.875	1:01	1:1.25
Average weight(mg)	525	524.6	525.2	525.4	524.5	525	524.7
LOD%	1.05	1.04	1.02	1.12	1.98	1.6	1.15
Bulk density(gm/ml)	0.429	0.464	0.472	0.498	0.478	0.548	0.566
Tap density(gm/ml)	0.574	0.821	0.896	0.638	0.548	0.998	0.653
Carr's compressibility index %	15.316	13.478	17.297	12.5	12.9	15.07	13.33
Hausner Ratio	1.331	1.069	1.0876	1.29	1.004	1.12	1.154
Friability %	1.029	0.014	0.014	0.073	0.2	0.043	0.13
Disintegration time(min)	18-20	8-9	2-3	1-1.5	1-1.5	1-2	1-2
Hardness(k_p)	20-21	16.5-17.5	16-17	10-11	7.5-8	7.5-8	7.5-8
Thickness (mn)	5.63	5.63	5.5	5.5	5.5	5.5	5.5

Table 3: Cumulative percentage of drug release of core tablets

Cumulative percentage of drug release							
Ratio(M S :osmotic)	Fo 1	Fo 2	Fo 3	Fo 4	Fo 5	Fo 6	Fo 7
Time(Hrs)	1:00	1:0.25	1:0.5	1:0.75	1:0.875	1:1	1:1.25
0.25	17.6	42.7	75.5	82.7	86	87.9	88.1
0.5	24.8	65.7	80.7	88.8	91.5	92.5	93.5
0.75	31.8	81.8	85.1	91.9	96	98.6	100.6
1	35	89.7	92.9	95.3	99.5	101.3	102.7

Figure 2: Cumulative percentage of drug release of core tablets



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Coating with semi-permeable polymer:

Core tablets were coated by using a Ganscons coating machine with a perforated pan. A solution of cellulose acetate in acetone at a concentration of (4%w/v), containing TEC at concentration of 10% of w/w of cellulose acetate, level of plasticizer (TEC) was used as the coating solution. To the acetone, slowly cellulose acetate added with proper mixing. In between, plasticizer was added drop wise and through mixing was done to dissolve the cellulose acetate. Addition of plasticizer in the coating solution improves film properties like film flexibility. The final coating solution was filtered through # 80 sieve. The composition solution used was mentioned in the below tabular form.

Table 4: Coating solution composition

INGREDIENTS	WEIGHT	CONCENTRATION (%)
Cellulose acetate	40gms	4%
Triethyl citrate	4 gms	0.4
Acetone	1000ml	Quantity sufficient

Core tablets of metoprolol succinate were place in coating pan and tablets were coated using the following parameters:

Pan rpm: 10-11
Coating solution spray rate: 4-5ml/min
In let temperature: 38°C
Outlet temperature: 28°C
Atomizer pressure: 1.0 kg/cm^2
Fan pressure: 1-0.75 kg/cm^2
Inlet air blower: 900 cpm
Outlet air blower: 1600 cpm

The coating solution was sprayed over the tablet bed by a spray gun till a desired weight gain was obtained on the active core tablets .Later the osmotic pump tablets were dried at 50°C for 1 Hr to remove the residual organic solvent

Evaluation of coated formulation:

The coated tablets were evaluated by visual inspection of the film smoothness, Uniformity of coating. The parameter like weight variation, thickness, diameter of the tablets recorded before and after coating, was measured by Verniercaliper. The measured parameters are :

Table 5: evaluation of coated formulation

Evaluation of coated formulation							
physical parameter	**Fo 1**	**Fo 2**	**Fo 3**	**Fo 4**	**Fo 5**	**Fo 6**	**Fo 7**
Ratio(M S :osmotic)	1:00	1;0.25	1:05	1:0.75	1:0.875	1:01	1:1.25
Average weight(mg)	546	545.5	545.8	546.1	545.7	545.8	545.2
Thickness(mn)	5.81	5.79	5.68	5.64	5.69	5.68	5.69

Characterization of the tablets

Fourier transform infrared spectroscopy

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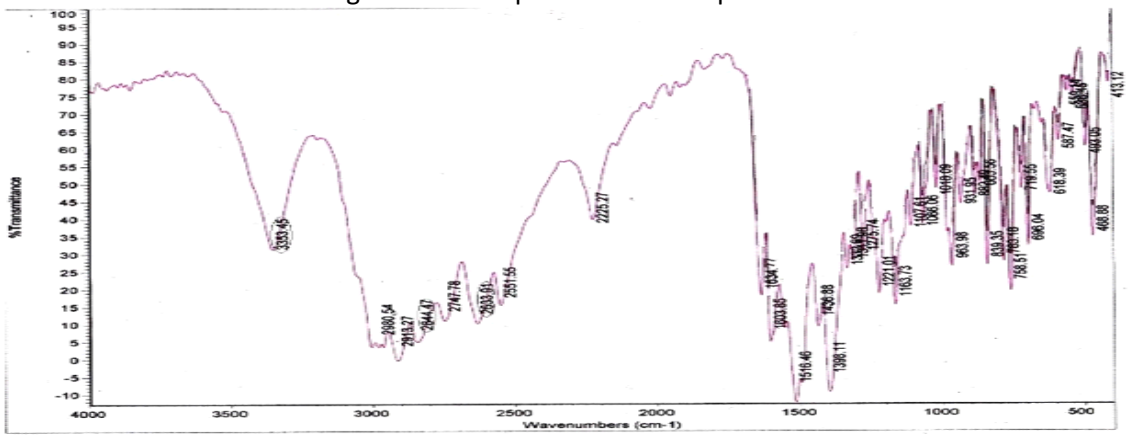
FT-IR analysis was carried out for pure drug and for formulations using KBr pellet method on Fourier transform infrared spectroscopy (FTIR) spectrophotometer type Shimadzu model 8033, USA, in order to ascertain compatibility between drug and polymers used.

Figure 3: FT-IR spectrum of metoprolol succinate



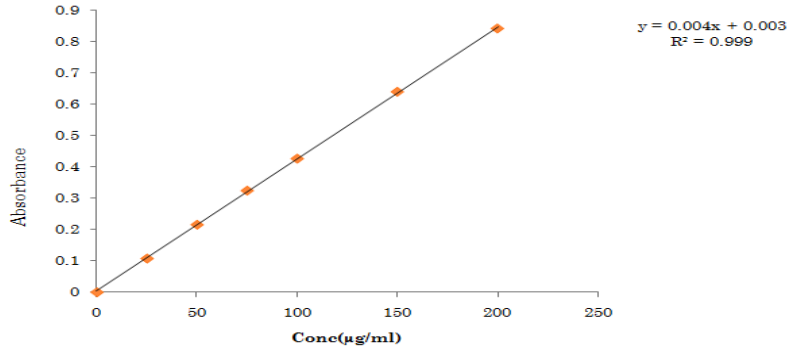
Functional group	Literature value	Observed value
-OH	3400-3200	3353.45
-NH-	2700-2250	2633.91
C-O-CH_3	2860-2810	2844.47

RESULTS AND DISCUSSION:

Table 6: Standard graph of metoprolol succinate in phosphate buffer pH 6.8

Concentration (µg/ml)	Absorbance
0	0
25	0.1074
50	0.2151
75	0.3235
100	0.4253
150	0.6383
200	0.8396

Figure 4: Standard response linearity with respect to concentration:



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The standard curve was prepared to determine the linearity of the absorbance across different concentrations and R^2 value was found to be 0.999

Effect of KCL as osmogen:

To investigate the effect of orifice size on the release of active material from the EOP tablets, the final coated tablets were drilled tablets to a known orifice of size 800µm, 1200 µm respectively manually with a pre-calibrated microdrill. All the batches of tablets with different orifice sizes were subjected to release studies.

Table 7: Release profile of Metoprolol succinate using different concentration of KCL at orifice size of 800µm

Cumulative percentage of drug release

Ratio(M S: smotic)	Fo 1	Fo 2	Fo 3	Fo 4	Fo 5	Fo 6	Fo 7
Time	1:00	1:0.25	1:05	1:0.75	1:0.875	1:01	1:1.25
1 Hr	0.2	1.5	2.4	2.8	2.8	2.6	5.4
2 Hr	1.3	3.9	5	8.5	12.6	5.5	7
4Hr	2.5	8.2	11	13.5	14.9	9	9.9
6 Hr	5.6	14.6	16	18	24.5	12.9	15.5
8Hr	9.2	19.5	21	24.2	25.2	24.9	24.5
12Hr	14.2	34.5	34	37	43.3	40.3	51.8
18Hr	26.5	58.9	60	65.3	68.5	68.4	84.2
24Hr	37.5	74.6	80	85.7	76.5	90.9	100.1

Figure 5:

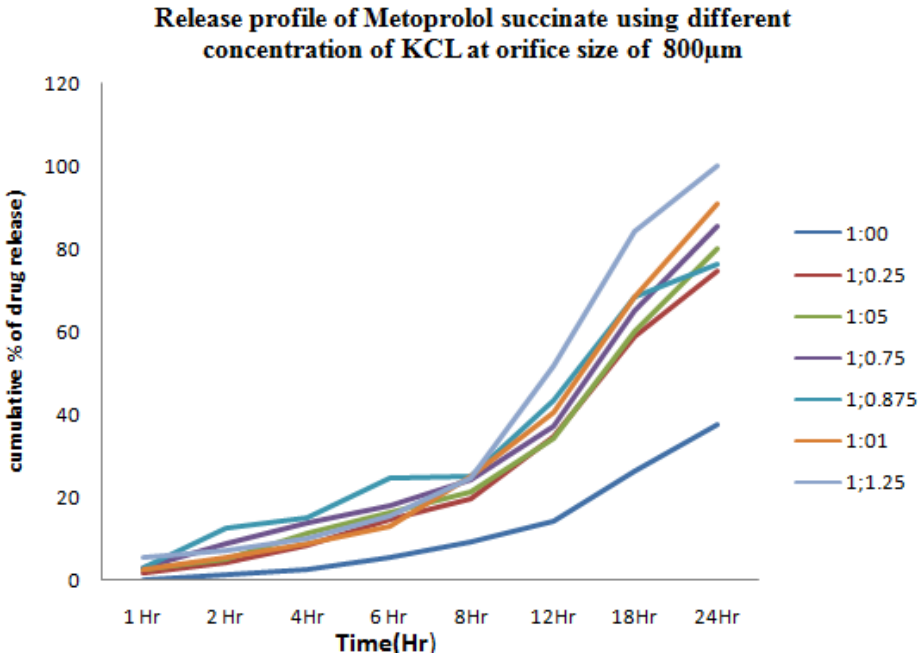

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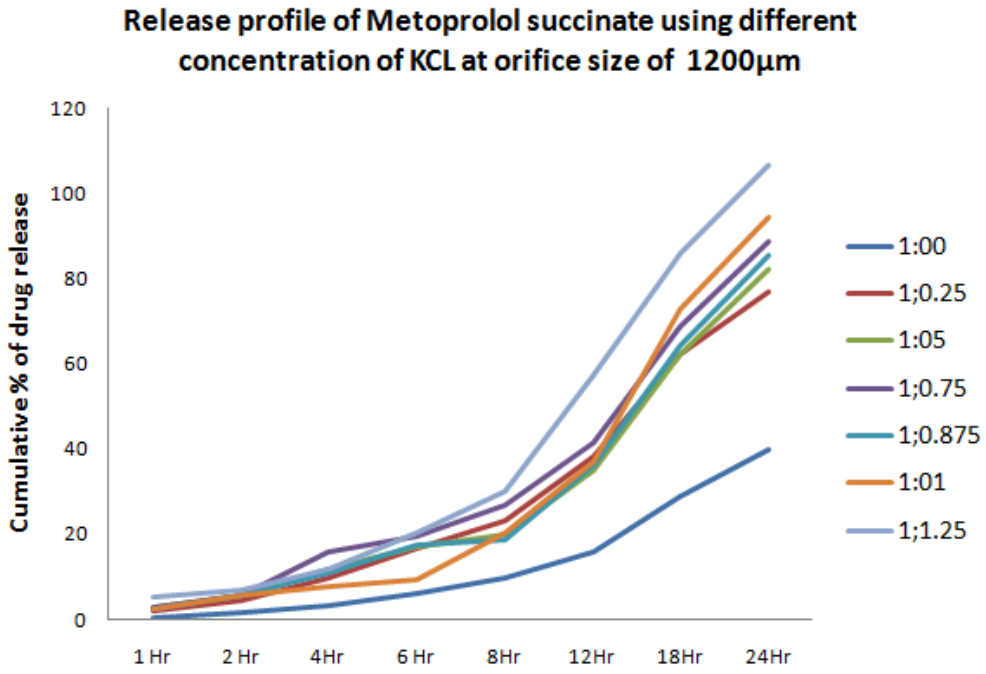
Table 8: Release profile of Metoprolol succinate using different concentration of KCL at orifice size of 1200µm

Time(Hrs)	Cumulative percentage of drug release						
Ratio(MS:osmotic)	Fo 1	Fo 2	Fo 3	Fo 4	Fo 5	Fo 6	Fo 7
Time(Hrs)	1:00	1:0.25	1:05	1:0.75	1:0.875	1:1	1:1.25
1 Hr	0.4	1.9	3	2.9	2.3	2.4	5.4
2 Hr	1.8	4.5	6	5.9	5.5	5.8	7
4Hr	3.2	9.5	12	15.8	10.9	7.5	11.7
6 Hr	6.2	16.5	17	19.5	17.2	9.3	20.4
8Hr	9.8	23	20	26.8	18.7	20.4	30.1
12Hr	15.8	38	35	41.5	36.2	37.1	57.5
18Hr	28.9	62	62	68.9	64.3	72.7	85.7
24Hr	39.7	76.8	82	88.7	85.5	94.3	106.4

Figure 6: Release profile of Metoprolol succinate using different concentration of KCL at orifice size of 1200 µm



As amount of KCL increased in the formulation, there is an enhancement in the release rate of drug from the EOP tablets.

Then the same formulation (Fo-6) containing increasing concentration of KCL as osmogens were drilled with an orifice size of 800µm, 1200µm and release studies were conducted and cumulative amounts released from the EOP formulation were calculated .Fo-6, with an orifice size of 800µm have release the drug to the desired rate when compared to the other orifice size of 1200µm. The release rate per hour was calculated for formulations table 24. Approximately it released nearly 63% of the drug by zero-order kinetics. Release rate per hour from Fo-6(800µm) were calculated, and it is within the required

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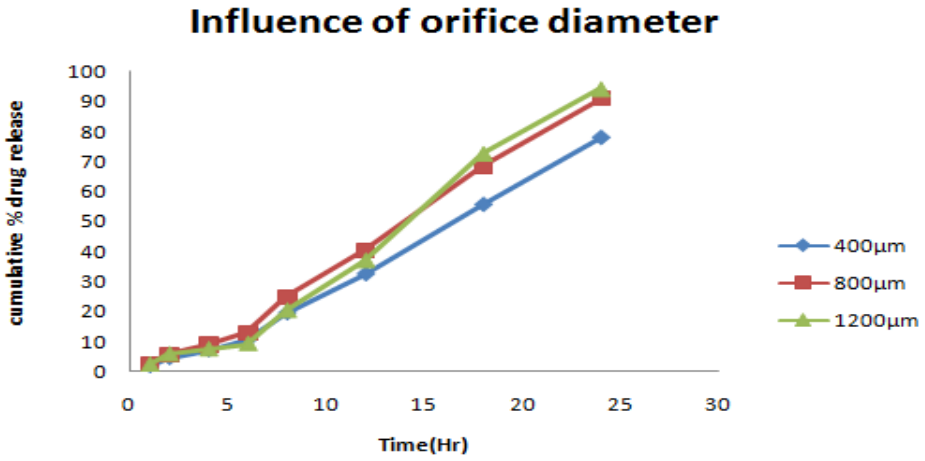
concentration of 7-10mg/hr. The formulation No-6 was considered to be best formulation at 800µm orifice size.

Table 9: Influence of orifice diameter on the dissolution profile of the metoprolol succinate

Cumulative percentage of drug release

Time	400µm	800µm	1200µm
1	1.9	2.6	2.4
2	4.6	5.5	5.8
4	7.2	9	7.5
6	10.6	12.9	9.3
8	19.5	24.9	20.4
12	32.5	40.3	37.1
18	55.6	68.4	72.7
24	77.9	90.9	94.3

Figure 7: Influence of orifice diameter on the dissolution profile of the metoprolol succinate



Influence of agitational intensity on drug release:

it is evident that the release rate is independent of the agitational intensity. The release rates obtained were quite comparable and there is no change in the release profiles obtained at different rpm. Therefore, it is clear that increase in rate of stirring did not significantly affect the release rate of the drug.

Table 10: Dissolution profile Influence of agitational of intensity on drug release (rpm)

Cumulative percentage of drug release			
Time(Hr)	**25rpm**	**50rpm**	**75rpm**
0	0	0	0
1	2.2	2.6	3
2	5.3	5.5	6
4	8.6	9	9.3

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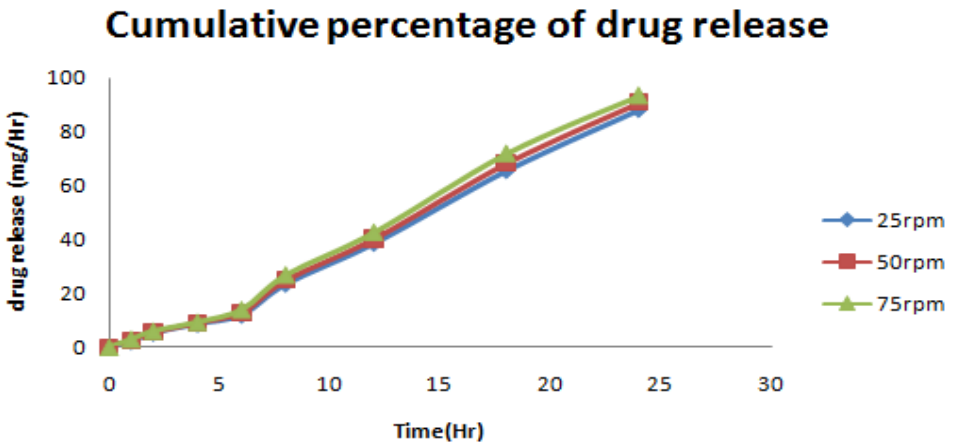
6	12	12.9	14
8	23.5	24.9	26.9
12	38.6	40.3	42.7
18	65.6	68.4	72
24	88.2	90.9	93.5

Figure8: Dissolution profile Influence of agitational of intensity on drug release (rpm)



Influence of membrane thickness on drug release profile:

The release rate of a drug is an oral osmotic pump is affected by the thickness of semi permeable membrane.

As the membrane thickness increased, the resistance of the membrane to water diffusion increased and inturn, the liquefaction rate of the tablet core decreased, resulting in the decrease of drug release rate. It was found that the coating solution containing 4% of CA having a thickness of 0.39 mm has release the drug in maximum zero-order fashion, when compared to the other membrane thickness over the core tablets. It is possible to alter the permeability of polymeric membrane by adding hydrophilic flux enhancers like plasticizers.

Table 11: Influence of membrane thickness on drug release profile

Cumulative percentage of drug release			
Time	**2%**	**4%**	**6%**
0	0	0	0
1	5	2.6	0.9
2	13.5	5.5	3
4	29.8	9	5
6	43	12.9	8
8	56	24.9	14.6
12	76	40.3	29
18	101.5	68.4	45.8
24		90.9	61

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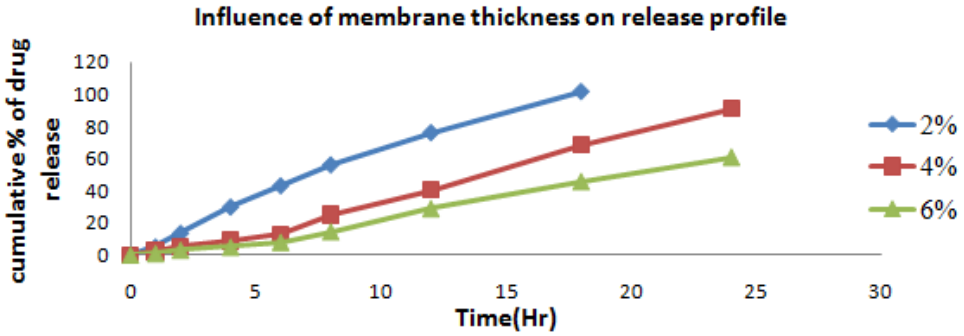
Figure9: Influence of membrane thickness on release profile



CONCLUSION

• The present study was carried out in order to develop controlled release tablets of metoprolol succinate by elementary osmotic pump for the treatment of myocardial infarction.
• FT –IR spectroscopic studies indicated that there are no drug excipient interactions.
• Tablets prepared by wet granulation method were found to be good without any chipping, capping and sticking.
• The hardness of the optimized formulation was found to be in the range of 7.5 to 8 kg/cm^2.
• The friability value of the optimized formulation was found to be in the range of 0.043%.
• Disintegration time was found to be in the range of 1-2 mins.
• Formulation F6 showed good results than the rest of the seven formulations in pre and post compression studies.
• Drug release from the systems followed zero-order kinetics and proved that the system could provide required controlled release rate up to 24 hours.

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