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Research Article

FABRICATION AND IN VITRO EVALUATION OF POROUS OSMOTIC PUMP BASED CONTROLLED DRUG DELIVERY OF METOPROLOL SUCCINATE

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ABSTRACT

Objective: The present aim of the work is that the osmotically controlled oral drug delivery system utilizes osmotic pressure for controlled delivery of active agents. It has gained wider acceptance due to drug release is independent of pH and physiological condition of the GIT. Metoprolol Succinate, a highly soluble drug has been used as a model drug and attempt has been made to control the release of drug by two different approaches; one using an osmotic agent and a swelling agent.

Methods: The core tablets were prepared by wet granulation technique and granules before compression were evaluated for micromeritic properties. The core tablets were coated with coating solution containing cellulose acetate, a pore former and a plasticizer to give good film properties. The effect of concentration of osmotic agent and swelling agent on *in vitro* release was studied and drug release depended on both these factors.

Results: The formulation variables like amount of pore former, effect of pH, agitational intensity on *in vitro* release from optimized formulation was evaluated and it was found that drug release directly depend on amount of pore former in the coating composition. The drug release was independent of pH and agitational intensity of the media. All the formulation release more than 60% of drug after 12 hrs and drug release from optimized formulation was found to follow zero order kinetics. The formulation was also found to be stable in terms of hardness, drug content and drug release after 3 months stability study.

Conclusion: The formulation F3 was found to be stable in terms of drug content and slight increase in hardness was observed and the i*n vitro* release profile of F3, initially and after3 months is almost comparable and there is no much difference observed.

Keywords: Osmotic pump, Controlled delivery, Metoprolol Succinate, Osmotic agent, Swelling agent.

INTRODUCTION

Drug delivery systems such as oral controlled-release dosage forms, transdermal patches, and implants are used to overcome these challenges[1]. Although the cost of these drug delivery technologies is considerable, it is substantially less than the cost of developing a new molecule[2-4]. Hence, a continued interest exists in developing novel drug delivery systems for the temporal and spatial delivery of active agents[5].Among the aforementioned technologies used to control the systemic delivery of drugs, osmotic drug delivery is one of the most interesting and widely applicable. Osmotic drug delivery uses the osmotic pressure of drugs or other solutes (called *Osmogents*) for controlled delivery of drugs.

CR delivery systems provide desired concentration of drug at the absorption site allowing maintenance of plasma concentrations within the therapeutic range and reducing the dosing frequency. A number of design options are available to control or modulate the drug release from a dosage form. Majority of per oral CR dosage forms fall in the category of matrix, reservoir, or osmotic systems. However, factors like pH, presence of food, and other physiological factors may affect drug release from conventional CR systems (matrix and reservoir).[7] Osmotic systems utilize the principles of osmotic pressure for the delivery of drugs. Drug release from these systems is independent of pH and other physiological parameters to a large extent and it is possible to modulate the release characteristics by optimizing the properties of drug and system. Alza Corporation of the USA (now merged with Johnson & Johnson, USA) was first to develop an oral osmotic pump and today also, they are leaders in this field with a technology named OROSTM. Osmotic delivery devices have changed considerably since Rose and Nelson developed the first osmotic pump for delivering drugs to animals.[8-9] From complex implantable devices to simple tablets, the extent of simplification and miniaturization has been remarkable. The osmotic delivery devices of today not only deliver drugs with moderate solubility, but also are capable of delivering drugs with solubility extremes. Furthermore, devices that deliver drugs as liquids (to deliver insoluble drugs and to enhance permeability) and that dispense subsaturated solutions of drugs are noteworthy developments.[10-15]

Advantages of osmotic drug delivery

Osmotic drug delivery systems for oral and parenteral use offer distinct and practical advantages over other means of delivery. The following advantages have contributed to the popularity of osmotic drug delivery systems:

- The delivery rate of zero-order (which is most desirable) is achievable with osmotic systems. Both in vitro and in vivo experiments have established this fact.
- Delivery may be delayed or pulsed, if desired.[15-17]
- For oral osmotic systems, drug release is independent of gastric pH an hydrodynamic conditions.
- Higher release rates are possible with osmotic systems compared with conventional diffusion-controlled drug delivery systems.
- The release rate of osmotic systems is highly predictable and can be programmed by modulating the release control parameters.[18-19]
- A high degree of in vivo–in vitro correlation (IVIVC) is obtained in osmotic systems.
- The release from osmotic systems is minimally affected by the presence of food in the gastrointestinal tract (GIT).
- These advantages are attributed to the design of osmotic systems. Osmotic systems have a high degree of IVIVC because the factors that are responsible for causing differences in release profiles in vivo and in vitro (e.g., variable pH, agitation) affect these systems to a much lesser extent. [20-25]

MATERIALS AND METHOD

Materials

Metoprolol Succinate is a gift sample of the Madras Pharmaceuticals, Mannitol is collected from S.D. Fine Chemicals, PVP K-30 and lactose are procured from Pharma BASF Limited, Microcrystalline Cellulose is collected from Pharma Arihant Trading Co.,Magnesium Stearate, Cellulose acetate, Sorbitol, Dibutyl Phthalate, Acetone Hydrochloric

acid Potassium chloride, Di-sodium hydrogen orthophosphate and potassium hydrogen orthophosphate anhydrous are collected from S.D. Fine Chemicals.

Formulation of the Osmotic Pump Tablets

Formulation of the osmotic pump tablets of Metoprolol Succinate containing different concentration of osmogent and a swelling agent. [25-27]

Core tablets of Metoprolol Succinate were prepared by wet granulation and batch size was kept as 200 tablets. The composition of the core tablets are given in Table 1. Metoprolol Succinate was mixed with mannitol, povidone, lactose and microcrystalline cellulose passed through 30 mesh screen. The blend was mixed for 10mins and the mixture was granulated with starch paste.

The resulting wet mass passed through 18 # sieve. The granules were dried at 60o C in hot air oven for 30 mins after which they were passed through 22 # sieve. These sized granules were then blended with magnesium stearate and talc for 10 mins in a polybag and finally compressed into tablets having average weight of 300mg using a Rimek minipress-1 single stroke tablet punching machine fitted with a 9mm round concave punches.

Coating of the osmotic pump tablets

The core tablets of Metoprolol Succinate were coated with cellulose acetate in an automated perforated pan (Ganscoater, India). The compositions of the coating solution used for coating tablets are given in Table 2. All the tablets were coated with coating solution A. Various components of the coating solution were added to the solvent in a sequential manner. The component added first was allowed to dissolve before the next component was added. Core tablets of Metoprolol Succinate were placed in coating pan. The rotating speed of the pan was kept 15-18 rev/min.

The coating was performed using spray gun and the spray rate of 3-5 ml/min. atomization pressure was kept 1kg/cm2 while outlet temperature was kept 40-45o C. Coating was continued until desired weight gain (10%) was obtained and tablets were dried at 50°C for 10 h before further evaluation.

Table 1: Composition of osmotic pump tablets of metoprolol succinate with osmogens and swelling agents

Formulation Ingredients	F1	F2	F3	F4	F5	F6
Metoprolol Succinate	50	50	50	50	50	50
Mannitol	70	100	130	100	100	100
Povidone	10	10	10	20	30	40
Lactose	70	50	40	60	40	30
Microcrystalline Cellulose	97	87	67	67	77	77
Magnesium Stearate	2	2	2	2	2	2
Talc	1	1	1	1	1	1
Starch	qs	qs	qs	qs	qs	qs
Purified water	qs	qs	qs	qs	qs	qs

Table 2: Composition of the coating solutions for metoprolol succinate osmotic pump tablets

Ingredients	Coat Solution A	Coat Solution B	Coat Solution C
Cellulose Acetate (gms)	3.0	3.0	3.0
Sorbitol (ml)	0.23(7.5%)	0.3(10%)	0.38(12.5%)
Dibutyl phthalate (ml)	0.45(15%)	0.45(15%)	0.45(15%)
Acetone:Purified water	Up to 100ml	Up to 100ml	Up to 100ml

Compositions given in terms of % W/W. Total solids in the coating compositions 4.0%.

RESULT AND DISCUSSION

Compatibility Studies

Compatibility studies of pure drug with excipients were carried out prior to the preparation of osmotic pump tablets. I.R spectra of pure drug and combination of drug and excipients were obtained, which are shown in Fig. 1. All the characteristic peaks of Metoprolol Succinate were present in Spectra thus indicating compatibility between drug and excipients. It shows that there was no significant change in the chemical integrity of the drug. wet granulation method. Before compression, the powder blends were subjected to pre-compression evaluation to determine the flow properties and the compressibility. The results of the pre-compression evaluation are as given below.

Bulk density and tapped density: The granules of different formulations were evaluated for Loose Bulk Density(LBD) and Tapped Bulk Density (TBD). Both the bulk density and tapped density results are shown in Table 3. The bulk density and the tapped density for all the formulations varied from 0.59 to 0.61 and 0.69 to 0.71 respectively.

The values obtained lies within the acceptable range and not a large difference exists between the bulk density and tapped density. This result helps in calculating the % compressibility of the powder.

Evaluation studies

The osmotic tablets of Metoprolol Succinate were prepared using

Compressibility index: The percentage compressibility of powder was determined using carr's compressibility index. Compressibility index lies within the range of 12.63 to 16.11.

All formulations show good compressibility. The results are shown in Table 3.

Angle of repose: Table 3 shows the results obtained for all the formulations. The values were found to be in the range of 26.11 to 28.58. All the formulation showed angle of repose below 30° which indicates a good flow property of the granule.

Thickness uniformity: The results of thickness for both coated and uncoated tablets were determined using a calibrated dial caliper and results are shown in Table 4. Tablet mean thickness (n=3) were almost uniform in all the formulations and values for core tablets ranged from 4.09±0.071mm to 4.16±0.074 mm and for coated tablets it ranged from 4.58±0.113 mm to 4.68±0.077 mm. The standard deviation values indicated that all the formulations were within the range and show uniform thickness.

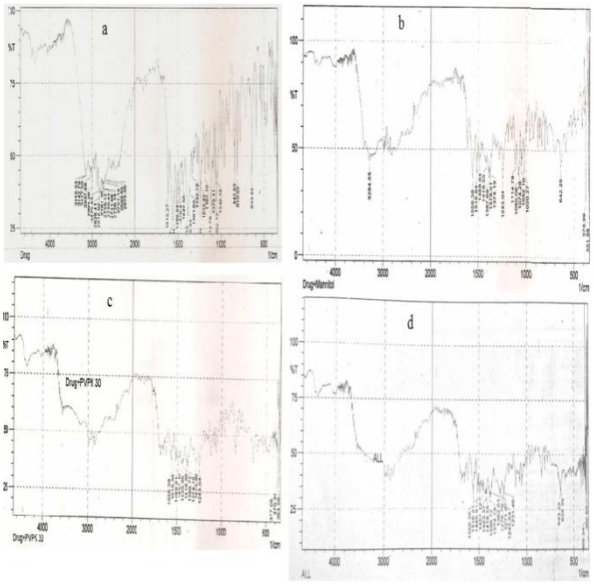

Fig. 1: a)FTIR studies of drug b) FTIR studies of drug+mannitol c) FTIR studies of drug+ PVP K30 d) FTIR studies of the optimised formulation

Weight variation test: Twenty tablets both core and coated were randomly selected from each formulation and evaluated. The average weight of each formulation is recorded and shown in Table 4. The values are almost uniform and lie within the USP specifications. The values of all the formulated core tablets ranged from 299.70±3.840mg to 301.80±4.514 mg and for coated tablets ranged from 325.4±4.694 mg to 327.10±4.204 mg. Thus all the formulations passed the test for weight variation.

Hardness test: The mean values of hardness of both core and coated tablets are as given in Table 4. The values of hardness for allthe formulated core tablet ranged from 5.970±0.217 kg/cm2 to 6.064±0.203 kg/cm2 and for coated ranged from 6.21±0.122 kg/cm2 to 7.98±0.216 kg/cm2. The lower values of standard deviation indicate that the hardness of all the formulations were almost uniform and possess good mechanical strength with sufficient hardness. Higher hardness of core tablets is indicating that the tablets will not break or crack during the tumbling motion when subjected to coating. Increase in hardness of the coated tablets is due to the coating, providing additional strength to the core.

Friability test: The friability values of all the formulated core tablets are given in Table 4. The values ranged from 0.0756 to 0.0986. All the values are below 1% indicating that the tablets of all formulations are having good compactness and strength to withstand the force during the coating operation without breaking.

Table 3: Precompression evaluation of the powder blends

Code	Bulk density	Tapped density	Hausner's ratio	Carr's index	Angle of repose
F1	0.59 ± 0.01	0.70 ± 0.01	1.19 ± 0.01	16.11 ± 0.90	26.72
F2	0.60 ± 0.01	0.69 ± 0.01	1.14 ± 0.04	12.63 ± 2.75	27.93
F3	0.60 ± 0.01	0.71 ± 0.01	1.17 ± 0.01	15.07 ± 0.73	28.58
F4	0.60 ± 0.01	0.69 ± 0.01	1.15 ± 0.03	13.73 ± 2.13	26.91
F5	0.61 ± 0.01	0.70 ± 0.02	1.15 ± 0.04	13.38 ± 2.63	27.73
F6	0.59 ± 0.01	0.70 ± 0.01	1.17 ± 0.03	15.28 ± 2.10	26.11

Table 4: Post compression evaluation of the osmotic pump tablets

Code	Thickness		Average weight		Hardness		Friability	Content uniformity (mg)
	Before coating	After coating	Before coating	After coating	Before coating	After coating		
F1	4.12±0.052	4.68±0.077	301.80±4.514	325.4±4.694	6.064±0.203	7.36±0.181	0.0756	49.94±2.44
F2	4.16±0.074	4.59±0.058	300.85±3.513	325.9±4.993	6.025±0.269	7.98±0.216	0.0927	48.94±3.08
F3	4.13±0.133	4.63±0.091	299.70±3.840	326.55±4.334	5.975±0.236	6.21±0.122	0.0986	49.29±2.96
F4	4.09±0.071	4.58±0.113	300.40±3.844	325.95±4.978	5.995±0.274	6.75±0.113	0.0867	49.04±1.93
F5	4.14±0.084	4.61±0.054	300.5±3.845	326.8±5.053	5.99±0.185	7.05±0.307	0.0885	48.96±2.45
F6	4.12±0.114	4.62±0.091	300.45±4.198	327.10±4.204	5.97±0.217	7.20±0.215	0.0956	49.09±3.18

Table 5: *In Vitro* release of Metoprolol Succinate of all the formulations

Time	F1	F2	F3	F4	F5	F6
0	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
0.5	1.95 ± 0.17	4.39 ± 0.72	5.29 ± 1.23	3.38 ± 1.17	2.412 ± 0.93	1.94 ± 0.82
1	3.91 ±0.34	6.83 ± 0.87	7.69 ± 1.17	4.83 ± 1.53	3.862 ± 1.95	3.39 ± 1.57
2	7.33 ± 0.40	10.26 ± 0.30	11.55 ± 1.14	7.73 ± 2.62	7.244 ± 1.86	6.78± 0.96
3	12.08 ± 0.64	15.31 ± 0.49	21.48 ± 1.29	12.41 ± 1.77	11.474 ± 1.77	11.96 ± 1.02
4	16.73 ± 0.53	21.82 ± 1.09	28.35 ± 0.67	20.68 ± 1.71	19.278 ± 1.97	18.41 ± 0.57
5	22.32 ± 1.75	29.72 ± 0.45	34.78 ± 1.94	28.50 ± 1.54	26.175 ± 3.26	23.04 ± 3.69
6	30.70 ± 0.96	38.09 ± 1.16	45.77 ± 1.19	34.96 ± 2.57	29.870 ± 2.28	27.65 ± 2.43
7	36.76 ± 2.39	45.55 ± 0.83	53.12 ± 1.10	38.67 ± 2.30	342.77 ±2.48	34.11 ± 1.52
8	43.76 ± 2.05	55.33 ± 1.07	64.14 ± 1.09	46.05 ± 2.43	6.320 ± 1.59	40.12 ± 3.25
9	54.02 ± 1.65	61.41 ± 0.42	72.43 ± 1.86	51.15 ± 2.69	48.325 ± 2.55	45.68 ± 1.56
10	60.11 ± 1.83	70.75 ± 0.74	83.46 ± 1.07	56.71 ± 2.49	53.878 ± 2.71	51.25 ± 2.10
11	69.46 ± 0.56	81.95 ± 1.31	89.95 ± 1.51	67.78 ± 5.88	61.730 ± 2.04	58.66 ± 1.87
12	74.64 ± 1.89	85.74 ± 1.83	91.87 ± 0.78	76.58 ± 3.49	68.673 ± 0.86	63.32± 1.58

Table 6: Comparison of the slope and the regression co-efficient for different models

Code	Zero Order	First Order	Higuchi plot	Best fit
F1	R =0.984	R =0.457	R =0.865	Zero Order
F2	R = 0.989	R = 0.898	R = 0.884	Zero Order
F3	R = 0.993	R = 0.898	R = 0.907	Zero Order
F4	R = 0.990	R = 0.920	R = 0.890	Zero Order
F5	R = 0.994	R = 0.953	R = 0.896	Zero Order
F6	R = 0.995	R = 0.963	R = 0.898	Zero Order

Table 7: Stability studies data for f3 formulation

Parameter	Initial	After 3 months
Hardness (kg/cm2)	6.21±0.122	7.14±0.315
Drug content (%)	49.29±2.96	48.14±3.32
Drug release at end of 12 hrs	91.87±0.78	94.61±1.80
Percentage drug release	91.87 ± 0.78	94.61 ± 1.80

Content uniformity test: The content uniformity was performed for all six formulations and results are shown in Table 4. Three replicates from each test were carried out. The mean and standard deviation of all the formulations are calculated. The drug content of tablets were found between 48.94±3.08 mg to 49.94±2.44 mg of Metoprolol Succinate. The cumulative percentage drug released by each formulation *in vitro* release studies were based on mean content of the drug present in the respective tablet.

The developed formulations of Metoprolol Succinate were subjected to *in vitro* dissolution studies using USP-Type I dissolution apparatus in two media i.e. pH 1.2(SGF) for 2 hrs and in pH 6.8 (SIF) after 2 hrs & up to 12 hrs in order to simulate the conditions prevalent in the gastrointestinal tract. The *in vitro* release profiles of formulation F1 to F3 containing different amount of osmotic agents are shown in Table 5.

F3 showed the highest release of 91.87±0.78% as compared to F1 and F2 which showed 74.64±1.89% and 85.74±1.83% respectively.

Similarly the *in vitro* release profiles of formulations F4 to F6 containing different amount of swelling agent are shown in Table 5. From the figure it is seen that the drug release is directly related to the concentration of swelling agent.

In the formulations F1 to F3 osmotic agent concentrations were varied and swelling agent concentration was kept constant. So from result it is seen that drug release is directly related to the concentration of osmogent present in the core tablets as the concentration of mannitol increases the cumulative amount of drug release is also increased as F3 released 91.87±0.78% which is due to the higher concentration of osmotic agent in the core tablet as compared to F1 and F2 which showed release of 74.64±1.89% and 85.74±1.83% respectively.Where as in the formulations from F4 to F6 the hydrophilic swelling polymer concentration were varied and osmotic agent concentration was kept constant. The use of hydrophilic polymer as release retardants has attracted special attention in the field of osmotic pressure controlled drug delivery system.

From the result it is seen that the drug release depends upon the concentration of swelling agent in the core tablets. Despite of higher solubility of Metoprolol Succinate in water the thickening of povidone K-30 solution in the hydrated tablets containing this drug retard release from the system. As the drug is highly soluble here an attempt has been made to retard to release of drug from the formulation. As the concentration of swelling agent increases the drug release from the tablet decreases. Formulation F6 containing highest amount of swelling agent showed slow release of drug from the tablets i.e. 63.31±1.58% as compared to F4 and F5 which showed release of 76.57±3.49% and 68.67±0.85% respectively.

All the formulations showed release of drug more than 60% at 12 hrs and F3 showed the better release amongst all, hence was considered as best optimized formulation and was further evaluated for effect of various formulation variables affecting drug release from the osmotic pump tablets which are discussed.

The data were evaluated for zero order, first order and Higuchi plot and the R2 value obtained are as shown in the Table -6. Release kinetics of Metoprolol Succinate for all the formulation seem to follow Zero order, because the values of regression coefficient obtained for zero order release profiles are higher as compared to first order and Higuchi plot.

The accelerated stability studies were carried out according to ICH guidelines. Optimized formulation F3 was packed in strips of aluminum foil laminated with PVC by strip packing and these packed formulation was stored in ICH certified stability chambers (Thermo labs, Mumbai) maintained at 40 oC and 75% RH (zone III conditions as per ICH Q1 guidelines) for 3 months. The tablets were evaluated for the drug content, hardness and *in vitro* release.

The samples were observed for any change on coating membrane. It was observed that coating membrane was devoid of any change in color or appearance of any kind of spot on it. It was also noted that membrane was free of any kind of microbial or fungal growth or bad odor. No change in the smoothness of the membran was noted. The drug content of the formulation was found to 48.14±3.32 mg which shows there is slight decrease in drug content but difference is insignificant.The in vitro release of the samples after 3 months storage compared with release profile of sample at zero day and the same was shown in Table-7. The formulation F3 was found to be stable in terms of drug content and slight increase in hardness was observed and the in vitro release profile of F3, initially and after3 months is almost comparable and there is no much difference observed. Thus the developed formulation is found to be stable for given storage conditions.

CONCLUSION

From the obtained results it can be concluded that, IR spectra of pure drug and with the excipients are identical and do not show any incompatibility, thus the excipients are compatible with the drug. Lower values of angle of repose below 30 indicate good flow properties of powder blends.Friability and hardness were within the pharmacopoeial limits thus showing good mechanical strength of tablets. Formulation F3 showed significant increase in drug release with increasing in concentration of osmotic agent. Thus drug release depends upon the amount of osmogent in the core tablet. Decrease in drug release in formulation with increase in concentration of swelling agent in core tablet indicates drug release depends on the amount of swelling agent in the formulation.Fromulation F3 showed significant increase in drug release with increasing concentration of poreformer in the coating material. The formulation F3 was found to be stable in terms of drug content and slight increase in hardness was observed and the i*n vitro* release profile of F3, initially and after3 months is almost comparable and there is no much difference observed.

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