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Research Article

FORMULATION AND EVALUATION OF METAPROLOL SUCCINATE EXTENDED RELEASE PELLETS

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ABSTRACT
The aim and of the present study is to develop a pharmaceutically stable and quality improved formulation of Metoprolol succinate extended release pellets. To achieve this goal various prototype formulation trials were formulated and the evaluated with respect to the various quality controls such as dissolution, assay and stability studies will be under taken. Metoprolol succinate is used in the treatment of hyper tension, angina pectoris (chest pain) and myocardial infarction. The study was undertaken with an aim to formulate Metoprolol succinate extended release pellets. The optimized batch MSER CF7 is made up of 7% wetting agent and 4.5% binder. The evaluation tests that were conducted for the pellets also showed satisfactory results.The best trial was optimized by comparing the drug release profile with the innovator and the MSER F7 showed better results compared to the other formulations and the evaluation studies were conducted for the MSER F7. It showed good results in formulation of stable dose.The pellets were evaluated for the flow properties, sieve analysis and accelerated stability studies for 3months. The pellets showed good flow properties and also showed uniform size which indicates uniform coating.Finally we concluded that the Metoprolol succinate pellets MSER F7 are prepared and these showed good physico-chemical properties and the dissolution results showed satisfactory results when compared with the innovator drug.
KEY WORDS: Metoprolol succinate, Extended release, Pellets.

INTRODUCTION

Drug Delivery System

The treatment of acute diseases or chronic illness has been achieved by delivery of drugs to the patients for many years. These drug delivery systems include tablets, injectables, suspensions, creams, ointments, liquids and aerosols. Today these conventional drug delivery systems are widely used. The term drug delivery can be defined as techniques that are used to get the therapeutic agents inside the human body [1,2].

Extended Release Drug Delivery System

Extended release system was introduced in the pharmaceutical market in the early 1950s by Smith Kline and French made an orally administered formulation of Dextroamphetamine sulphate by incorporating the drug pellets coated with wax. Extended release dosage forms release drug slowly, so that plasma concentrations are maintained at a therapeutic level prolonged period of time (usually 12hrs) extended drug action at a pre-determined rate by maintaining a relative constant, effect drug level in the body with concomitant minimization of undesirable side effects that are associated with a saw tooth kinetic pattern of conventional release [3,4].

Methods of Preparing Pellets

Compaction and drug layering are the most widely used pelletization techniques in the pharmaceutical industry. Of the compaction techniques, extrusion and spheronisation is the most popular method and in drug layering the wurster process is most widely used. Recently melt pelletization has been used frequently in making compaction pellets using a different type of equipment, for example: a high-shear mixer. Other pelletization methods such as globulation, balling and compression are also used in development of pharmaceutical pellets but in a limited scale[5].



Figure 1: Layered pellet internal characteristics and layered pellet

Powder Layering

In this technique the dry powders of the drug an its excipients are mixed thoroughly and they are deposited as the successive layers over the inert core. the binding liquids are used for the deposition of the dry powder layers. This process takes place mostly in a specialized equipment known as the spheroniser. The container should be made of solid walls. There should be no perforations in the container walls. The walls should be of smooth in texture so that the powder should not be attached to the walls of the container[6].

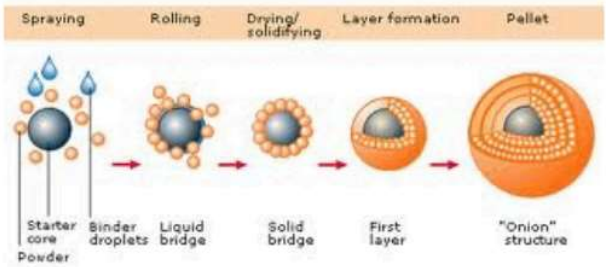


Figure 2: Powder layering

Solution/Suspension Layering

In this technique the drug along with its excipients are weighed accurately and are mixed in a solution to form a uniform suspension. Then this mixture is coated on the inert core materials. The coating should be done in such a way that the inert cores are uniformly coated with the drug suspension. this process involves mainly the wurster process. These involves the equipments such as coating pans, centrifugal granulators and fluidized bed processors. mostly the inert core material used is the sugar spheres. The efficiency of the process and the quality of the pellets produced are related to the type of equipment used and the conditions or parameters that are used during the coating process[7,8].

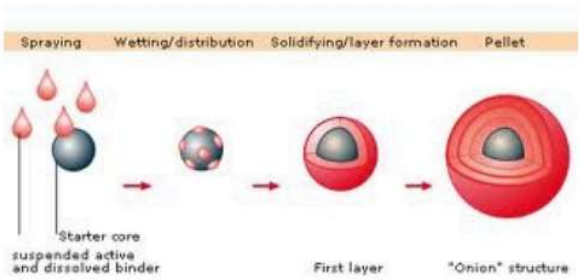


Figure 3: solution or suspension layering

Pelletization by Extrusion and Spheronisation

In this process the drug along with its excipients are taken and mixed together to form mass. Then these are converted to form the extrudes through the process extrusion and then these are converted into small beads like structures through a process known as spheronisation. Nowadays equipments are available by which both the extrusion and spheronisation are done simultaneously in a single equipment. Through his process beads as fine as 0.6 mm can be obtained[9].

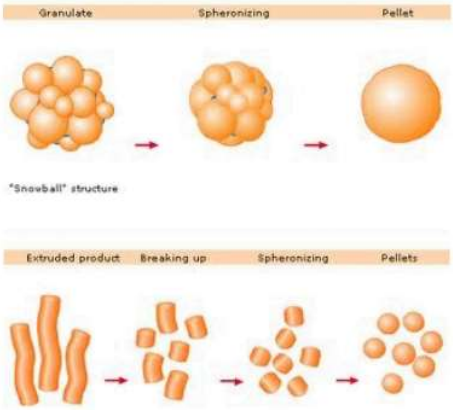


Figure 4: Pelletization by spheronisation and extrusion

Aim

The aim and of the present study is to develop a pharmaceutically stable and quality improved formulation of Metoprolol succinate extended release pellets. To achieve this goal various prototype formulation trials were formulated and the evaluated with respect to the various quality controls such as dissolution, assay and stability studies will be under taken.

Formulation Development

Metoprolol succinate extended release capsules were prepared. The process was displayed in the below flow chart.

Table 1: Composition of the core pellets in the formulation trials

S.No	Ingredients (mg)	MSER CF1	MSER CF2	MSER CF3	MSER CF4	MSER CF5	MSER CF6	MSER CF7	MSER CF8
1	Metoprolol succinate	50	50	50	50	50	50	50	50
2	Manitol	12.5	12.5	12.5	12.5	12.5	125	125	12.5
3	Sodium lauryl sulphate	10	9.5	9	8.5	8	7.5	7	6.5
4	Sugar spheres (24/30)	25	25	25	25	25	25	25	25
5	HPMC	1.5	2	2.5	3	3.5	4	4.5	5
6	Yellow oxide	1	1	1	1	1	1	1	1
	Total (mg)	100	100	100	100	100	100	100	100

Table 2: Composition of the coating material for the optimized core pellet

S.No	Ingredients	MSER F1	MSER F2	MSER F3	MSER F4	MSER F5	MSER F6	MSER F7	MSER F8
7	Ethyl cellulose (mg)	2%	2.5%	3%	3.5%	4%	4.5%	5%	5.5%
8	Iso propyl alcohol (ml)	65ml	85ml	100ml	115ml	135ml	150ml	165ml	185ml

In- Vitro Drug Release Studies

The in vitro drug release studies were performed for marketed product using dissolution medium as 6.8 pH Phosphate buffer volume 900 ml at 50 rpm, USP II apparatus. By using UV-spectrophotometer at 224 nm[10,11].

Dissolution Parameters

- Media - 6.8 pH phosphate buffer.
- Apparatus - USP II (paddle)
- RPM - 50
- Amount of media - 500 ml
- Temperature -37°C ±0.5
- Time - Upto 20hrs for polymer coated pellets. Upto 1hr for drug coated pellets.

RESULTS AND DISCUSSION

Evaluation of drug coated Pellets (Core Pellets)

Table 4: Physical characters of Metoprolol succinate optimized core pellets

S.No.	Characteristics	Results
1.	Physical appearance	Yellowish crystalline spheres.
2.	Dimension	1.2mm-1.8mm
3.	Hardness	6kg/cm^2
3.	Bulk density	0.38 gm/ml
4.	Tapped density	0.448 gm/ml
5.	Compressibility index	15.147%
6.	Hausner's ratio	1.178%
7	Angle of repose	33.47°

Assay of pellets

Table 5: Assay of core pellets

Character	MSER CF1	MSER CF2	MSER CF3	MSER CF4	MSER CF5	MSER CF6	MSER CF7	MSER CF8
Assay	98.56%	97.68%	98.36%	97.34%	98.64%	98.48%	99.32%	98.86%

Table 6: Dissolution studies of drug coated pellets (core pellets)

S.No	Time interval (min)	Cumulative % drug release							
		MSER CF1	MSER CF2	MSER CF3	MSER CF4	MSER CF5	MSER CF6	MSER CF7	MSER CF8
1	15	38.75	36.85	33.86	31.48	27.85	26.89	25.36	24.48
2	30	78.46	75.86	74.84	68.78	58.78	55.35	64.86	56.56
3	45	98.56	98.84	95.46	93.85	88.46	83.42	82.73	81.56
4	60	99.65	99.32	98.76	98.82	99.45	99.64	99.65	98.87

Evaluation of Polymer Coated Pellets

Table 7: Physical characters of optimized Metoprolol succinate polymer coated pellets

S.No.	Characteristics	Results
1.	Physical appearance	Yellowish crystalline powder.
2.	Dimension	1.6mm-2mm
3.	Hardness	9kg/cm^2
3.	Bulk density	0.37gm/ml
4.	Tapped density	0.425gm/ml
5.	Compressibility index	11.793%
6.	Hausner's ratio	1.1317%
7	Angle of repose	28.53

Table 8: Assay of polymer coated pellets

Character	MSER F1	MSER F2	MSER F3	MSER F4	MSER F5	MSER F6	MSER F7	MSER F8
Assay	99.45%	99.78%	100.43%	99.65%	99.86%	99.48%	99.86%	99.48%

Dissolution profile

Standard graph for metoprolol succinate

Table 9: Standard plot of Metoprolol succinate

S.No	Concentration (µgm/ml)	Absorbance
1	5	0.172
2	10	0.328
3	15	0.476
4	20	0.662
5	25	0.791
6	30	0.9696

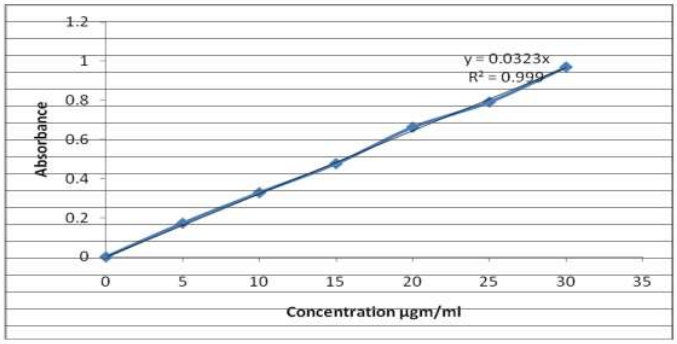


Figure 5: Standard curve of metoprolol succinate

Slope=0.032 R^2=0.999

Table 10: Comparative dissolution profile for Metoprolol succinate prepared formulations MSER F1 to MSER F8

S.No	Cumulative % drug release			
	1st hr	4th hr	8th hr	20th hr
MSER F1	48.5	72.3	92.4	99.8
MSER F2	41	69.83	86	98.67
MSER F3	36.5	57.67	83	98
MSER F4	29.4	52.6	79.4	97.9
MSER F5	26.83	47.5	76	97.83
MSER F6	21	37.67	69.167	98.167
MSER F7	13.83	33.67	56.67	97.33
MSER F8	8.67	27	47	94.5

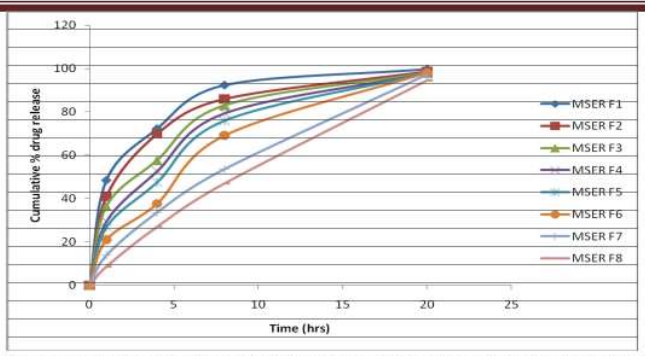


Figure 6: Comparative dissolution profile for prepared formulations MSER F1 to MSER F8

Table 11: *In-Vitro* Drug Release kinetics for MSER 7

S.No	*Zero order* data		Higuchi's data		Peppa's data	
	Time (hrs)	Cumulative % release	Square root of time	Cumulative % release	Log time	Log cumulative % release
1	0	0	0	0	0	0
2	1	13.83	1	13.83	0	1.140
3	4	33.67	2	33.67	0.602	1.527
4	8	56.67	2.83	56.67	0.903	1.753
5	20	96.667	4.47	96.667	1.301	1.985

SUMMARY AND CONCLUSION

- Metoprolol succinate is used in the treatment of hyper tension, angina pectoris (chest pain) and myocardial infarction. The study was undertaken with an aim to formulate Metoprolol succinate extended release pellets.
- The optimized batch MSER CF7 is made up of 7% wetting agent and 4.5% binder. The evaluation tests that were conducted for the pellets also showed satisfactory results.
- The best trial was optimized by comparing the drug release profile with the innovator and the MSER F7 showed better results compared to the other formulations and the evaluation studies were conducted for the MSER F7. It showed good results in formulation of stable dose.
- The pellets were evaluated for the flow properties, sieve analysis and accelerated stability studies for 3months. The pellets showed good flow properties and also showed uniform size which indicates uniform coating.
- Finally we concluded that the Metoprolol succinate pellets MSER F7 are prepared and these showed good physico-chemical properties and the dissolution results showed satisfactory results when compared with the innovator drug.

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