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# Formulation and Evaluation of Sustained Release Metoprolol Succinate Matrix Tablets by Direct Compression Process using Kollidon SR

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**Abstract:** The aim of the present study was to formulate the Metoprolol Succinate sustained release matrix tablets by cost saving and production efficient process. Among various tablet manufacturing process, direct compression is the simplest and cost saving process. Different trials were formulated and evaluated using different concentrations of directly compressible grade and controlled release polymer of Kollidon SR to match the reference product dissolution profile. Dissolution studies were conducted using USP recommended conditions.
**Key Words:** Sustained release, Kollidon SR, Metoprolol Succinate, direct compression process.

## Introduction and Experimental

Oral route is the most preferred route for administration of drugs. Tablets are the most popular oral formulations available in the market and preferred by the patients and physicians alike. In long-term therapy for the treatment of chronic disease conditions, conventional formulations are required to be administered in multiple doses, and therefore have several disadvantages[1]. Controlled release (CR) tablet formulations are much desirable and preferred for such therapy because they offer better patient compliance, maintain uniform drug levels, reduce dose and side effects, and increase safety margin for high potency drugs[2].

Metoprolol Succinate, beta1- selective adrenergic receptor blocking agent used in the management of hypertension, angina pectoris, cardiac arrhythmias, myocardial infarction, heart failure, hyperthyroidism and in the prophylactic treatment of migraine. The half-life of drug is relatively short approximately 4-6 hrs and in normal course of therapy drug administration is required every 4-6 hrs, thus warrants the use of sustained release formulation for prolong action and to improve patient compliance[3].

Metoprolol Succinate is absorbed throughout the GIT. The drug is freely soluble at any pH, hence judicious selection of release retarding excipients is necessary for achieving constant invivo release. The most commonly used method of modulating the drug release is to include it in a matrix system[4]. Matrix based CR tablet formulations are the most popular and easy to formulate on a commercial scale in an industry. The matrix tablets can be prepared via wet granulation or by direct compression[5].

In the present study direct compression method was selected using direct compressible grade controlled release polymer of Kollidon SR. The manufacturing of matrix tablets by direct compression is a cost saving simple process bearing a high attractivity. Most of the controlled release polymers (i.e HPMC, Alginates,

Xanthan gum) possess poor flow properties, hence unsuitable for direct compression process.

In this study, influence of different ratio of polymer concentration on drug release was evaluated by keeping the drug substance concentration constant and altering the controlled release polymer concentration & similarly also evaluated the influence of drug substance concentration in matrix tablet formulation on drug release characteristics by keeping the polymer concentration constant and altering the drug substance concentration.

Kollidon SR is a relatively new matrix retarding agent consisting of 80% polyvinyl acetate and 20% polyvinylpyrrolidone. With its excellent flowability, this formulated combination allows sustained release dosage forms to be manufactured by the simple direct compression process.

Kollidon SR is made by spray drying of the mixture of polyvinylacetate (PVAc) and polyvinylpyrrolidone (PVP) (PVAc:PVP = 4:1). The polyvinylpyrrolidone component gradually leaches out of the matrix during dissolution thereby creating the pores for the active to diffuse out. The compressed polyvinylacetate component maintains tablet core structure during dissolution.[6]

**Materials:**

Metoprolol Succinate was obtained from Ipca Loratories Lab Ltd, Mumbai. The Kollidon SR was obtained from BASF AG. Colloidal anhydrous silica (Aerosil 200) was obtained from Degussa; Magnesium Stearate was obtained from Amishi. Solvents and all other reagents used were of analytical grade.

**Preparation of Matrix Tablet:**

Metoprolol Succinate matrix tablets were prepared by direct compression process. Metoprolol Succinate, Kollidon SR and Aerosil 200 were sifted through ASTM #40 mesh and blended for 15 minutes in an Octagonal blender. Magnesium Stearate was sifted through ASTM #80 mesh and transferred into above blender and lubricated for 5 minutes.

Above lubricated blend was compressed in Cadmach double rotary tablet punching machine (M/S. Cadmach Machinery Co. Pvt. Ltd, Ahmedabad) using appropriate size of standard concave punches.

In the prototype formulations from MS-001 to MS-006, the concentration of drug was kept constant (i.e. 95 mg of Metoprolol Succinate equivalent to 100 mg of Metoprolol Tartrate), release controlling polymer (i.e. Kollidon SR) was varied from 25% to 150%. Glidant (i.e. Aerosil 200) was kept near to 1% and Lubricant (i.e. Magnesium Stearate) was kept near to 0.5% in all formulations.

The composition of various formulations is shown in Table 1.

**Evaluation of Matrix Tablets:**

**Physical tests:**

Initially the lubricated blend was evaluated for density parameters and compressibility index was calculated to estimate the flow properties, since flow properties of the final blend is a critical parameter for direct compression approach. The physical parameters of the lubricated blend were provided in table no 2.

The compressed tablets were characterized by their physical properties. The average tablet weight was determined from 20 tablets (USP, 2007). Hardness of the tablets was tested using a Monsanto tablet hardness tester. Friability of the tablets was determined in Roche friabilator. Tablet friability was calculated as the percentages of weight loss of 20 tablets after 100 rotations (USP, 2007). The physical parameters for the compressed tablets were provided in table no 3.

**Dissolution studies:**

In vitro drug release studies from prepared matrix tablets were conducted for a period of 20 hours using six stations USP type 2 apparatus at 37 ± 0.5°C, with paddle at 50 rpm and 500 mL of dissolution medium using pH 6.8 phosphate buffer. Samples of 10 mL were taken from the dissolution medium at appropriate intervals, after filtration and appropriate dilution; the absorbencies were measured by UV spectrophotometer (Shimadzu, Japan) at 274 nm. The amounts of the drug present in the samples were calculated with the help of appropriate calibration curves constructed from reference standards. Similarly, dissolution study was conducted for the reference product (i.e Seloken XL, Batch No: SXHJ001, Manufacturer: AstraZeneca) and compared with the test products. The dissolution profiles for the trials were provided in table no 4.

## Results and Discussion

The physical parameters of the lubricated blend (i.e. Table 2) from all the trials were evaluated. From the data it was observed that, low bulk density and poor flow properties for trials formulated with low concentration of Kollidon SR (i.e. MS-001, MS-002 & MS-003).

The physical parameters of the compressed tablets (i.e. Table 3) from all the trials were evaluated. There was improvement in the physical parameters of the compressed tablets was observed by increasing in the polymer concentration. Low hardness and little high friability were observed with trials formulated with low concentration of polymer and high concentration of drug substance (i.e. MS-001, MS-002 & MS-003); this is due to low bulk density and low compressibility nature of Metoprolol succinate drug substance.

The drug release pattern of formulated trials of Metoprolol Succinate Matrix Tablets from MS-001 to MS-006 is shown (Table No.4). From the data it was

evident that there is a proportional release control with increase in the concentration of the Kollidon SR. From these formulations MS-005 was found to be best formulation because the release pattern of this batch was within the USP limit and further the f2 value is 73 (i.e. more than 50).

From the above observations we can conclude that Kollidon SR can be utilized for effective production of controlled release Metoprolol Succinate matrix tablets by direct compression process using an optimum concentration for desired release profile and with good quality parameters.

**Table 1: Formula of Metoprolol Succinate Matrix Tablets**

| **Batch No** | **MS-001** | **MS-002** | **MS-003** | **MS-004** | **MS-005** | **MS-006** |
|---|---|---|---|---|---|---|
| **Ingredients** | **Mg/tablet** | | | | | |
| Metoprolol succinate | 95.0 | 95.0 | 95.0 | 95.0 | 95.0 | 95.0 |
| Kollidon SR | 23.8 | 47.5 | 71.3 | 95.0 | 118.8 | 142.5 |
| Aerosil 200 | 1.2 | 1.4 | 1.7 | 1.9 | 2.1 | 2.4 |
| Magnesium Stearate | 0.6 | 0.7 | 0.8 | 0.9 | 1.0 | 1.2 |
| **Total tablet weight** | **120.6** | **144.6** | **168.8** | **192.8** | **216.9** | **241.1** |

**Table 2: Physical evaluation of Lubricated blend**

| **Batch No** | **MS-001** | **MS-002** | **MS-003** | **MS-004** | **MS-005** | **MS-006** |
|---|---|---|---|---|---|---|
| **Parameter** | **Results** | | | | | |
| Bulk density (g/ml) | 0.28 | 0.30 | 0.33 | 0.37 | 0.47 | 0.53 |
| Tapped density (g/ml) | 0.41 | 0.40 | 0.44 | 0.45 | 0.55 | 0.62 |
| Compressibility index | 32 | 25 | 25 | 18 | 15 | 8 |

**Table 3: Physical evaluation of Metoprolol Succinate Matrix Tablets**

| **Batch No** | **MS-001** | **MS-002** | **MS-003** | **MS-004** | **MS-005** | **MS-006** |
|---|---|---|---|---|---|---|
| **Parameter** | **Results** | | | | | |
| Average weight (mg) | 121.5 | 145.3 | 171.2 | 193.4 | 217.2 | 242.8 |
| Hardness ($kg/cm^2$) | 2-4 | 6-9 | 6-10 | 6-12 | 7-15 | 8-19 |
| Friability (%) | 0.54 | 0.37 | 0.32 | 0.25 | 0.16 | 0.12 |

**Table 4: Dissolution profiles of Metoprolol Succinate Matrix Tablets**

| **Time in hours** | **USP limits** | **Seloken XL** | **MS-001** | **MS-002** | **MS-003** | **MS-004** | **MS-005** | **MS-006** |
|---|---|---|---|---|---|---|---|---|
| 1 | NMT 25% | 10 | 46 | 32 | 24 | 21 | 13 | 8 |
| 4 | 20 - 40% | 28 | 77 | 61 | 46 | 38 | 33 | 19 |
| 8 | 40 - 60% | 51 | 100 | 88 | 76 | 65 | 54 | 38 |
| 20 | NLT 80% | 98 | 100 | 100 | 101 | 100 | 99 | 78 |
| f2 value | | | 20.4 | 28.3 | 38.5 | 49.3 | 73.0 | 44.6 |

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