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# Formulation and In-Vitro Evaluation of Sustained Release Tablet of Isosorbide -5- Mononitrate by Porous Osmotic Technology

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The objective of the present study was to develop sustained release tablet of Isosorbide Mononitrate by porous membrane osmotic technology. The drug is mainly indicated for the treatment of Stable and unstable angina pectoris, acute myocardial infarction and heart failure. The tablets were prepared by wet granulation method. The granules were evaluated for angle of repose, bulk density, tapped density, compressibility index and Hausner ratio. The tablets were subjected to thickness, hardness, friability, weight variations, and drug content by assay and *in vitro* dissolution studies. The drug release from Isosorbide Mononitrate sustained release was carried out in 1.2 N HCl, 4.5 pH acetate buffer and 6.8 pH phosphate buffer for 24hrs. The granules showed satisfactory flow properties, compressibility index and drug content. All the tablet formulations showed acceptable pharmaceutical properties. Formulation variables like type (PVP, PEG 4000 and HPMC) and level of pore former (0-55%, w/w of polymer), percent weight gain were found to affect the drug release from the developed formulations.The optimized formulation showed the highest f2 (f2 = 76.4) value. The drug release from the developed formulation was independent of pH and agitational intensity. The similarity factor f2 was applied between the optimized formulation and the theoretical dissolution profile.

*Keyword:* Coating; extended release; Isosorbide mononitrate; Osmotic pressure; Osmotic pump; Stability.

**INTRODUCTION:** The aim of the work is to investigate the possibility of obtaining a prolonged, relatively constant level of isosorbide-5-mononitrate.Isosorbide -5-Mononitrate has long elimination half-life of 4-5 hours in comparison of isosorbide Di-nitrate. Despite of this long elimination half-life, Isosorbide Mononitrate is prescribed 2-3 times/day for prophylactic treatment of angina leads to poor patient complaints and development of tolerance. Present studies investigate the possibility for the development of sustained release tablet of ISMN, to reduce the side effect, dosing frequency and improve patient compliance. Keeping these factors in view it is aim to formulate and evaluate SR tablet of 20 mg, to provide a controlled and predictable release of isososrbide-5-mononitrate,

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which is an organic nitrate used as anti-anginal drug for the treatment of stable and unstable angina pectoris, acute myocardial infarction for once daily administration. The present study, aim towards the development of sustained release of drug from the tablet by using osmotic technology. Theoretically design zero – order delivery pattern for the release the drug from the formulation. Considering different formulation variables and the selection of the optimized formulation from the drug release profile, considering the cost of drug by reducing the drug dose and increasing its effectiveness and deliver drug at near constant rate.

## Preparation of Osmotically Controlled Sustained release tablets:

Core tablets of Isosorbide Mononitrate were prepared by wet granulation method. The formulation is composed of lactose as diluents, sodium chloride as osmogent, PVP dissolved in isopropyl alcohol as granulating agent. Magnesium stearate and silicon dioxide were finally added as glident and lubricant. All the powders were passed through 30 mesh sieve. In the formulation of core tablet Isosorbide Mononitrate and Lactose were mixed for few minutes.Then powdered Sodium chloride were added and continued mixing for 5 minutes. To the power mixture PVP dissolved in Isopropyl alcohol were added as granulating agents and continued mixing for 10 minutes. To the mix, magnesium stearate and colloidal silicon dioxide were added and mixed for 10 minutes. The granules formed were coated with eudragit dissolved in Isopropyl alcohol coating solution and are dried. Then the granules were compressed to round tablet having an average weight of 150 mg using a multi-stroke tablet punching machine. The core tablets of Isosorbide Mononitrate were coated in standard coating pan. The composition of coating solution includes HPMC, PVP, PEG 4000, Propylene Glycol and ethylene dichloride. The components were added in the solvent mixture in sequential manner. Core tablets were placed in the coating pan, rotated at a low speed of 15-20 rpm and heated air was passed through the tablet bed. Coating process started once the outlet temperature reached optimal. The coating solutions were sprayed at specific rate and maintained the inlet temperature at 45-50ºC.Then the coated tablets were dried at 50ºC before further evaluation. Development of various tablet formulations are given in Table no:

**Table no: 1 Formulations of Core Tablets:**

| Serial No: | Ingredients | Quantity for 1 tablet (150 mg) |
|---|---|---|
| 1 | Isosorbide Mononitrate | 20.00 |
| 2 | Lactose | 65.00 |
| 3 | Sodium Chloride | 35.00 |
| 4 | PVP | 10.00 |
| 5 | Magnesium Stearate | 2.00 |
| 6 | Silicon dioxide | 0.50 |
| 7 | Eudragit | 5.00 |
| 8 | Isopropyl Alcohol | q.s |

## RESULTS AND DISCUSSION

### Pre formulation studies:

### Organoleptic properties:

These tests were performed as per the procedure given in 2.1.1 in material and method part. The results are given in table below:

**Table: 3Determination of organoleptic properties:**

| Test | Specification/ limits | Observations |
|---|---|---|
| Colour | White to off - white powder | White to off - white powder |
| Taste | Bitter | Bitter |
| Odour | Almost odourless | Almost odourless |

**Table no: 2Development of various Tablet Formulations:**

| Ingredients | FI | F2 | F3 | F4 | F5 | F6 | F7 |
|---|---|---|---|---|---|---|---|
| Ethyl Cellulose | 3.95 | 3.66 | 3.30 | 3.00 | 2.74 | 2.74 | 2.74 |
| HPMC | - | - | - | - | - | 1.52 | - |
| PEG 4000 | - | - | - | - | - | - | 1.52 |
| PVP | - | 0.37 | 0.82 | 1.20 | 1.52 | - | - |
| Propylene Glycol | 1.05 | 0.98 | 0.88 | 0.80 | 0.73 | 0.73 | 0.73 |
| Ethanol | 38.00 | 38.00 | 38.00 | 38.00 | 38.00 | 38.00 | 38.00 |
| Dichloro methane | 57.00 | 57.00 | 57.00 | 57.00 | 57.00 | 57.00 | 57.00 |

## 2. Physical characteristics:

### a) Angle of repose:

It was determined as per procedure given in 2.1.2. in materials and method parts. The results are given in table below:

**Table no: 4 Determination of Angle of repose of powder drug:**

| S.No. | Material | Angle of repose(°) | Average angle of repose(°) |
|---|---|---|---|
| 1 | Isosorbide Mononitrate | 41.25 | 41.116 |
| 2 | | 40.8 | |
| 3 | | 41.3 | |

**Table no: 5 Determination of Angle of repose of granules:**

| S.No. | Material | Angle of repose(°) | Average angle of repose(°) |
|---|---|---|---|
| 1 | Isosorbide Mononitrate Granules ready for compression for 20mg label claim | 28.39 | 28.260 |
| 2 | | 27.86 | |
| 3 | | 28.53 | |

The results of the tablet indicate that the granules ready for compression showing fair to good flow ability with the angle of repose values ranging from 27.86 to 28.53 according to the readings and are better than that of powder drug.

### b) Bulk density and Tapped density:

It was determined as per procedure given in 2.1.2 in materials and methods part. The results are given in table below:

### Table no: 6 Determinations of Bulk Density and Tapped Density of powder drug:

| S. No | Material | Bulk Density ($g/cm^3$) | Average Bulk Density ($g/cm^3$) | Tapped Density ($g/cm^3$) | Average Tapped Density ($g/cm^3$) |
|---|---|---|---|---|---|
| 1 | Isosorbide Mononitrate | 0.362 | 0.360 | 0.486 | 0.484 |
| 2 | Isosorbide Mononitrate | 0.356 | | 0.478 | |
| 3 | Isosorbide Mononitrate | 0.363 | | 0.488 | |

### Table no 7: Determinations of Bulk Density and Tapped Density of Granules:

| S. No | Material | Bulk Density ($g/cm^3$) | Average Bulk Density ($g/cm^3$) | Tapped Density ($g/cm^3$) | Average Tapped Density ($g/cm^3$) |
|---|---|---|---|---|---|
| 1 | Granules | 0.769 | 0.764 | 0.801 | 0.804 |
| 2 | Granules | 0.761 | | 0.804 | |
| 3 | Granules | 0.763 | | 0.809 | |

### C) Powder Compressibility:

It was determined as per procedure given in 2.1.2 in materials and methods part. The results are given in table below:

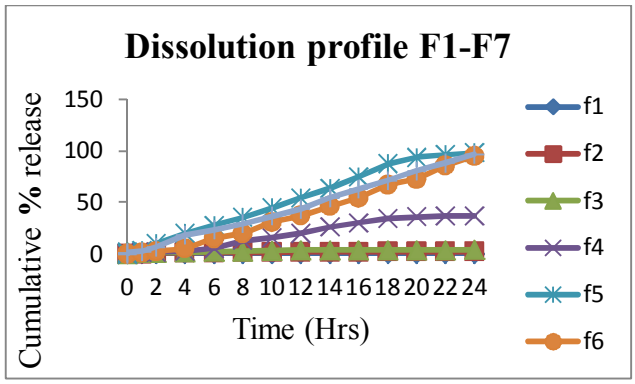
### Table no 8: Determination of Powder compressibility:

| Materials | Compressibility Index | Hausner Ratio |
|---|---|---|
| Isosorbide Mononitrate (Bulk Powder) | 4.82 | 1.02 |
| Isosorbide Mononitrate (Granules) | 5.62 | 1.08 |

### 3. Physical Compatibility Test:

It was determined as per procedure given in 2.1.3 in materials and methods part. The results are given in table below:

### Cumulative %Drug Release profile of all tablets formulations:




### Evaluation of tablet formulation (Physical characteristics):

The tablet is evaluated for the following parameter as given below in table no:

1. Weight variation test was conducted as per specifications.
2. Thickness and length using a Vernier Calipers.
3. Hardness test was performed using a Monsanto Hardness Tester.
4. Friability test was performed using a Roche Friabilator.
5. Drug content (Assay by UV Spectromertic method.

**Table.8: Comparison of Cumulative % Drug release of optimized formulation with marketed SR tablet (Monit SR)**

| Time(Hrs) | Marketed SR tablet (Monit SR) | Optimized formulation (F5) |
|---|---|---|
| 0 | 0 | 0 |
| 0.5 | 2.8 | 1.900 |
| 1 | 4.7 | 3.600 |
| 2 | 11.5 | 9.804 |
| 4 | 20.9 | 19.708 |
| 6 | 29.3 | 27.612 |
| 8 | 36.1 | 35.214 |
| 10 | 45.9 | 44.318 |
| 12 | 52.9 | 54.422 |
| 16 | 72.45 | 74.915 |
| 20 | 88.26 | 93.519 |
| 24 | 100.03 | 98.122 |

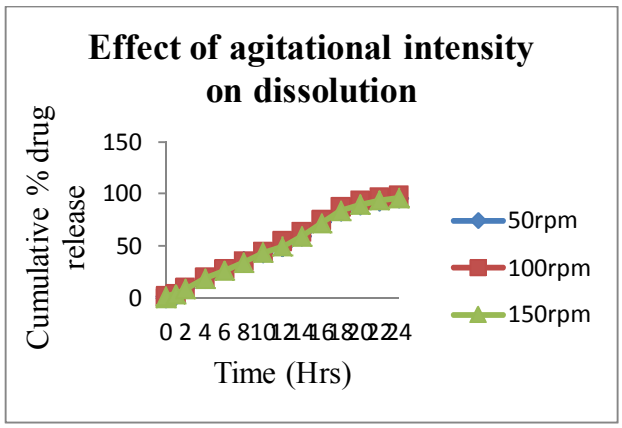
**Table: 7 Evaluation of tablet formulations:**

| Parameter | F1 | F2 | F3 | F4 | F5 | F6 | F7 |
|---|---|---|---|---|---|---|---|
| Uniformity of weight | Pass | Pass | Pass | Pass | Pass | Pass | Pass |
| Hardness ($Kg/cm^2$) | 6.82 | 7.24 | 7.63 | 7.31 | 7.35 | 7.39 | 6.87 |
| Thickness (mm) | 3.52 | 3.53 | 3.56 | 3.62 | 3.58 | 3.52 | 3.66 |
| Diameter | 6.51 | 6.50 | 6.52 | 6.51 | 6.50 | 6.49 | 6.50 |
| Friability (%) | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 |
| Drug Content (%) | 96.203 | 94.45 | 95.542 | 93.454 | 98.403 | 97.087 | 96.976 |

**Table-10 Cumulative % Drug release profile of optimized formulation on agitational intensity:**

| Time(Hrs) | 50 rpm | 100 rpm | 150 rpm |
|---|---|---|---|
| 0 | 0 | 0 | 0 |
| 0.5 | 1.87 | 1.900 | 1.92 |
| 1 | 2.58 | 3.600 | 3.65 |
| 2 | 9.79 | 9.804 | 8.8114 |
| 4 | 18.6988 | 19.708 | 18.7143 |
| 6 | 27.604 | 27.612 | 26.343 |
| 8 | 35.208 | 35.214 | 34.367 |
| 10 | 43.311 | 44.318 | 43.456 |
| 12 | 49.145 | 54.422 | 49.543 |
| 16 | 69.86 | 74.915 | 68.004 |
| 20 | 84.456 | 93.519 | 84.689 |
| 24 | 96.045 | 98.122 | 96.174 |

**Fig: 11. Cumulative % Drug release profile of optimized formulation on agitational intensity:**




## SUMMARY AND CONCLUSION

Sustained release tablets of Isosorbide Mononitrate were prepared by wet granulation technique. *In vitro* studies showed formulation F5 was well suited to be sustained release formulation. The coating solutions were prepared by using various polymers and pore formers, meets all the ideal characteristics to formulate in the form of sustained release drug delivery system. Under pre formulation study, the organoleptic properties were complied with the BP specification. Physical properties such as bulk density and tapped density were more in case of granules ready for compression than that of Isosorbide-5 Mononitrate raw powder. The compatibility evaluation was performed by FT-IR spectroscopy analysis. The study implies that the drug and polymers were compatible with each other. There were no interactions found between the drug and the polymers.F5 formulation was optimized as it complied with all the pharmacopoeial specifications. The physical parameters like thickness, diameter, hardness, friability, weight variations were carried out. The assay was carried out for optimized formulation and the result was found to be 98.403%. The drug release from the developed formulations was independent of pH and agitational intensity of the release media. It was found that the drug release increases with increasing the level of pore former (PVP), the membrane became more porous after coming in contact with the aqueous environment. The drug release was found to decrease with the increase in the weight gain of the membrane. The drug release was found to be more with PVP than with HPMC, Ethyl Cellulose and PEG4000. The similarity factor f2 was applied between the dissolution profile of optimized batch and the theoretical dissolution profile, which also indicate a decent similarity between both dissolution profiles. Stability studies were carried out by keeping the Sustained release tablets at room temperature (25ºC ± 2ºC/ 60% ± 5% RH) and at accelerated temperature (40ºC ± 2ºC/ 75% ± 5% RH) in stability chamber for 60 days. The result of stability studies conducted on F5 revealed no change in physical appearance, drug content and *in vitro* dissolution profile, hence F5 formulation was found to be stable at tested temperature.

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