# FORMULATION AND EVALUATION OF SOLID DISPERSION BASED FORMULATION OF MONTELUKAST SODIUM

***[1]MANISHA GAIROLA, [2]Mrs. Archana Rautela, [3]Ms. Ankita**

Gyani inder singh institute of professional studies, dehradun, Uttarakhand.

**ABSTRACT**

Solid dispersion is defined as a dispersion which is involving formation of drugs eutectic mixtures with water soluble carriers by melt of their physical mixtures. The solid dispersion is one or more active ingredient dispersion in inert carrier and matrix at solid state that is prepared by melt, fusion, solvent, or melt solvent method. For the permeability and oral bioavailability drug solubility is key point. For oral asthma administration there have some drugs which solubility have a problem to development a suitable formulation. The solid products are composed by at least two different components and it is produced by hydrophobic drug and hydrophilic matrix. The dispersion matrix can be either in a crystalline or amorphous form. Then the drug can be dispersed, in amorphous particles or in a crystalline particle. Montelukast is an orally active compound that binds with high affinity and selectivity to the CysLT1 receptor (in preference to other pharmacologically important airway receptors, such as the proteinoid, cholinergic, or β-adrenergic receptor). Montelukast inhibits physiologic actions of LTD4 at the CysLT1 receptor without any agonist activity. For enhancing the bioavailability, solid dispersion is formed. A following carrier is used PEG400 and HPMC in appropriate ratio with montelukast sodium. The demonstrated that one of the quick discharging measurements structure for inadequately water dissolvable montelukast by utilizing solid dispersion innovation.

**KEYWORDS:** Dispersion, Eutectic mixture, Hydrophobic.

## INTRODUCTION

Asthma is a most common chronic inflammatory disease of the airways, characterized by hyper responsiveness to a variety of stimuli. The role of circadian rhythms in the pathogenesis and treatment of asthma indicates that airway resistance increases progressively at night in asthmatic patients. Circadian changes are seen in normal lung function, which reaches a low point in the early morning hours.[1] The worsening of asthma at night commonly referred to as nocturnal asthma (NA). A drug delivery system administered at bedtime. Asthma is chronic respiratory disorder that causes difficulty in breathing when the airways become inflamed and narrow.

It is usually caused by allergies. The condition can be managed by medication but sometimes, severe asthma attacks can be fatal.[2]

**Causes**

In most cases of asthma in children, multiple triggers or precipitants exist, and the patterns of reactivity may change with age. Treatment can also change the pattern. Certain viral infections, such as respiratory syncytial virus (RSV) bronchiolitis in infants, predispose the child to asthma [3]

- **Respiratory infections:** Most commonly, these are viral infections. In some patients, fungi (eg,allergic bronchopulmonary aspergillosis), bacteria (eg, mycoplasmata, pertussis) or parasites may be responsible. Most infants and young children who continue to have a persistent wheeze and asthma have high immunoglobulin E(IgE) production and eosinophilic immune responses (in the airways and in circulation) at the time of the first viral (Upper Respiratory tract infection). They also have early IgE-mediated responses to local aeroallergens [4].
- **Allergens:** In patients with asthma, 2 types of broncho constrictor responses to allergens exist. [5]
- **Early asthmatic** responses occur via IgE-induced mediator release from mast cells within minutes of exposure and last for 20-30minutes.
- **Late asthmatic** responses occur 4-12 hours after antigen exposure and result in more severe symptoms that can last for hours and contribute to the duration and severity of the disease. Inflammatory cell infiltration and inflammatory mediators play a role in the late asthmatic response. Allergens can be foods, household inhalants (e.g., animal allergens, molds, fungi, cockroach allergens, dust mites), or seasonal outdoor allergens (e.g., mold spores, pollens, grass,trees)

**Treatment of the patients**

Medications used to treat asthma are generally divided into 2 main categories: relievers and controllers. Relievers are best represented by the inhaled short-acting β2-agonists. These quick-acting bronchodilators are used to relieve acute intercurrent asthma symptoms, only on demand and at the minimum required dose and frequency. Inhaled ipratropium bromide is less effective, but is occasionally used as a reliever medication in patients intolerant of short-acting β2-agonists. Controllers (or preventers) include anti-inflammatory medications, such as inhaled (and oral) glucocorticosteroids, leukotriene-receptor antagonists, and anti-allergic or inhaled nonsteroidal agents, such as cromoglycate and nedocromil. These agents are generally taken regularly to control asthma and prevent exacerbations. Inhaled glucocorticosteroids are the most effective agents in this category.[6]

**Introduction to Solid Dispersion:**

The solvency to allude to how effectively something dissolved in water or another fluid. Salt has high dissolvability, effectively dissolving in water, while oil has low solvency in water, and sand isn't at all solvent in water. The job of dissolvability in pharma field the solvency help to choose the best dissolvable for a medication or a combination of a medication. The biopharmaceutics classification system to separate the medications based on their solvency and permeability.[7]

**Mechanism of dissolution:**

The release profile of drug management using solid dispersions achieved by the carrier manipulation and solid dispersion particles properties. Parameters, such as, composition, drug crystallinity, carrier molecular weight particle wettability and porosity that successfully controlled is produce improvements in bioavailability.

**Techniques for solubility enhancement:-**

Solubility improvement techniques can be categorized in to physical modification, chemical modifications of the drug substance, and other techniques.[8]

**Physical Modifications:-**

**Particle size reduction:**

1. micronization,
2. sonocrystallisation,
3. Nano suspension,
4. Super critical fluid process.

**Modification of the crystal hab**

1. polymorphs,
2. Pseudo-polymorphs.

**Montelukast Sodium**

Physiochemical properties:

| | |
|---|---|
| Molecular Formula | $C_{35}H_{35}ClNNaO_3S$ (Martin AR 1998). |
| Molecular Weight | Average – 608.17g (Martin AR 1998).<br>Monoisotopic- 607.192 |
| Category | Antiasthmatic (Martin AR 1998). |
| IUPAC Name | 2-[1-[1(R)-[3-[2(E)-(7-Chloroquinolin- 2-yl) vinyl] phenyl]-3-[2-hydroxy- 1- methyl ethyl) phenyl] propyl sulfanyl methyl] cyclopropyl] acetic acid sodium salt. |
| Appearance | Off white to pale yellow colored powder. |
| Pka | Strongest Acidic – 4.4 (ChemAxon)<br>Strongest Basic- 3.12 (ChemAxon) |
| LogP | 8 (chemAxon) |
| Solubility | Soluble in water, methanol and ethanol and practically insoluble in acetonitrile (chemAxon) |
| Melting Point | 148 to $153^0$C (Martin AR 1998). |
| Half Life | 2.7-5.5 hrs. |

## CARRIERS USED FOR SOLID DISPERSIONS

### 1. Poly Ethylene Glycol:

Poly ethylene glycol is asynthetic, hydrophilic, biocompatible polymer with across the board use in biomedical and different applications. PEGs are synthesized utilizing a ring-opening polymerization of ethylene oxide to deliver an expansive scope of molecular weight and molecular weight dissemination (polydispersity); notwithstanding, discrete poly ethylene glycol are synthesized with a single, explicit molecular weight[10]

### 2. Hydroxy propyl methyl cellulose (HPMC):

Portrayal Hypromellose, or hydroxypropyl methylcellulose (HPMC) is a semisynthetic, inert, and viscoelastic polymer when disintegrate in water that forms a colloid solution. It work as thickening agent, covering polymer, bio adhesive, solvency enhancer in solid dispersion, and in binder during the time spent granulation and in adjusted release formulations.[9]

## MATERIALS AND METHODS:

Montelukast sodium and other ingredients were provided by our college. All reagents are pharmaceutical aid, Distilled water used for all the experiments.

| Ingredients | Manufacturer |
|---|---|
| Montelukast sodium | M/s Aptuit Laurus Private Ltd., Hyderabad(provided by college) |
| Mannitol | Coloron, UK |
| Croscarmellose sodium | Maple Biotech Pvt. Ltd. |
| MCC PH 101 | FMC Biopolymer, USA |
| MCC PH 102 | FMC Biopolymer, USA |
| Hydroxypropyl cellulose | Merck limited, Mumbai |

## EVALUATION OF PRE-COMPRESSION PARAMETERS:

1. **Angle of repose**
2. **Bulk density**
3. **Tapped density**
4. **Compressibility index**

| Formulation code | Bulk density (gm/ml) (± SD) | Tapped density (gm/ml) (± SD) | Hausners' ratio (± SD) | Angle of repose (± SD) |
|---|---|---|---|---|
| **F1** | 0.576±0.094 | 0.667±0.120 | 1.26 | 29.56±0.04 |
| **F2** | 0.565±0.089 | 0.667±0.91 | 1.20 | 26.21±0.079 |
| **F3** | 0.578±0.064 | 0.714±0.069 | 1.21 | 27.89±0.051 |
| **F4** | 0.526±0.101 | 0.676±0.034 | 1.26 | 29.19±0.067 |
| **F5** | 0.476±0.093 | 0.588±0.113 | 19.08±0.093 | 1.23 | 27.97±0.084 |
| **F6** | 0.516±0.099 | 0.666±0.074 | 21.02±0.089 | 1.26 | 25.86±0.044 |
| **F7** | 0.50±0.108 | 0.558±0.07 | 14.9±0.107 | 1.17 | 25.52±0.021 |
| **F8** | 0.486±0.114 | 0.555±0.108 | 14.23±0.034 | 1.16 | 27.61±0.099 |

**DEVELOPMENT OF SOILD DISPERSION BASED FORMULATIONS**

**1. PEG Based Solid Dispersion**

Solid dispersion of Montelukast was obtained by melting method. Solid dispersion was prepared by heating the PEG to 70℃ followed by addition of montelukast with constant stirring. Further molten mixture was allowed to cool down to room temperature. The solid product was ground in a mortar at room temperature and then sieved (sieved no 60). Different formulations were prepared by varying the drug and polymer ratio (1:1, 1:2, 1:3 and 1:4)

**EVALUATION:**

**Table: 2 observation table for solubility profile of PEG 4000 based solid dispersion.**

| Drug Ploymer ratio | Abs.1 | Abs.2 | Abs.3 | Solubility (mg/ml) |
|---|---|---|---|---|
| **1:1** | 0.078 | 0.076 | 0.075 | 0.083±0.0005 |
| **1:2** | 0.375 | 0.365 | 0.376 | 0.352±0.004 |
| **1:3** | 0.110 | 0.115 | 0.109 | 0.116±0.003 |
| **1:4** | 0.091 | 0.095 | 0.094 | 0.99±0.001 |

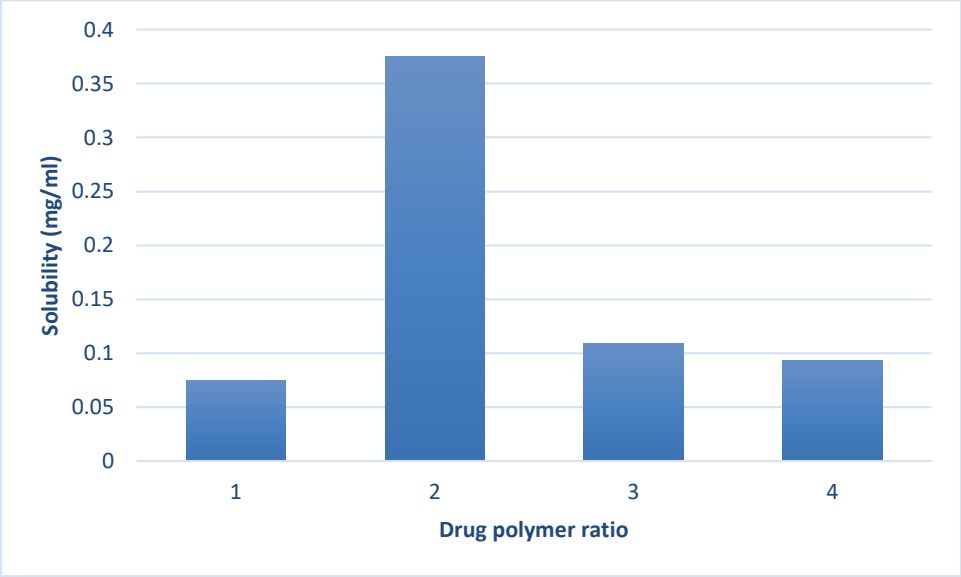


**Fig 1: Solubility profile of PEG 4000 based solid dispersion**

## 2. Poloxamer Based Solid dispersion

**Table 3: observation table for solubility profile of Poloxamer 407 based solid dispersion.**

| **Drug Ploymer ratio** | **Abs.1** | **Abs.2** | **Abs.3** | **Solubility (mg/ml)** |
|---|---|---|---|---|
| **1:1** | 0.378 | 0.378 | 0.376 | 0.35±0.0001 |
| **1:2** | 0.272 | 0.280 | 0.280 | 0.62±0.004 |
| **1:3** | 0.099 | 0.092 | 0.097 | 0.10±0.003 |
| **1:4** | 0.071 | 0.075 | 0.074 | 0.081±0.002 |

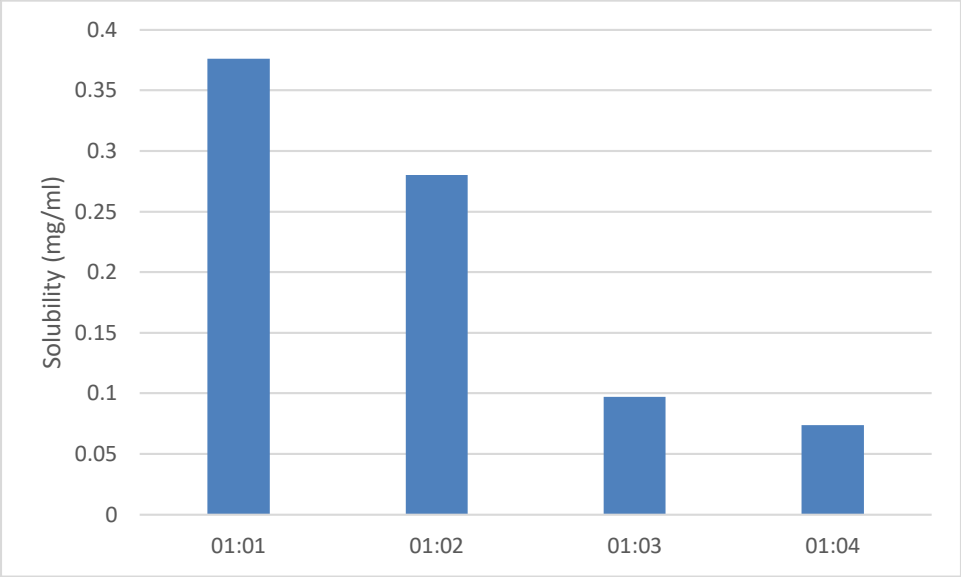


**Fig 2: Solubility profile of Poloxamer 407 based solid dispersion**

## EVALUATION OF POST COMPRESSION PARAMETER:

| Formula | Avg. weight(mg) | Thickness(mm) | Hardness(kg/cm$^2$) | Friability (%) |
|---|---|---|---|---|
| **F2** | 301±0.13 | 4.31±0.0004 | 3.2±0.15 | 0.98 |
| **F3** | 297.0±0.22 | 4.29±0.0011 | 3.0±0.13 | 0.38 |
| **F4** | 297.4±0.13 | 4.28±0.0032 | 3.4±0.14 | 0.29 |
| **F5** | 298.0±0.01 | 4.25±0.0032 | 3.2±0.02 | 0.23 |
| **F6** | 301.5±0.24 | 4.26±0.0053 | 3.2±0.15 | 0.18 |
| **F7** | 302.2±0.15 | 4.25±0.0058 | 3.1±0.12 | 0.14 |
| **F8** | 301.4±0.27 | 4.28±0.0033 | 3.1±0.01 | 0.20 |

**In Vitro release profiles study of different formulation:**

**Table 4: In Vitro release profiles study of different formulation:**

| Sampling time (minutes) | Drug release profile (% drug release) | | | | | | |
|---|---|---|---|---|---|---|---|
| | F2 | F3 | F4 | F5 | F6 | F7 | F8 |
| 10 | 80±0.91 | 82±0.53 | 82±0.44 | 85±0.25 | 88±0.24 | 86±0.29 | 86±0.90 |
| 15 | 84±0.83 | 88±0.84 | 86±0.57 | 89±0.52 | 91±0.29 | 90±0.36 | 89±0.83 |
| 20 | 93±0.29 | 91±0.69 | 90±0.77 | 92±0.74 | 96±0.41 | 92±0.74 | 90±0.55 |
| 30 | 95±0.59 | 93±0.73 | 95±0.24 | 94±0.05 | 98±0.21 | 96±0.27 | 93±0.29 |

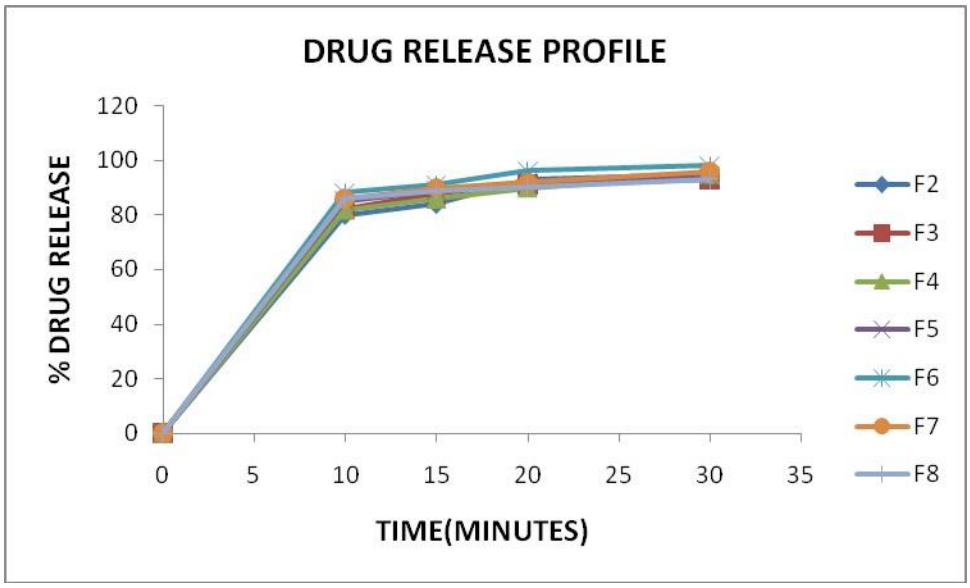


**Fig 3:** Comparative *In Vitro* drug release profile of Formulation F2 to F8

**RESULT AND CONCLUSION:**

Montelukast sodium is a leukotriene receptor antagonist used in maintenance and treatment of asthma. The formulations were evaluated for pre-compression, post-compression parameters and the values were found to be prescribed limits for all formulations. The angle of repose indicates passable to good flow properties for all the formulations.

The compressed tablets were evaluated for various physical parameters such as description, weight variation, thickness, hardness, friability, disintegration time and *in-vitro* dissolution test. The results were presented in Table 8.4and 8.5. Weight variation was found in the range of 297 mg to 306 mg,

Thickness was found in the range of 4.12 mm to 4.42 mm, Hardness was found in the range of 8 to 11 kp for the all the formulations indicating good mechanical strengths. The percentage friability of all formulations was found in the range of 0.01% to 0.25%, and the value the below 1% is an indication of tablet with good mechanical resistance. The disintegration time of all formulations were found to be in the range of1-1.5min. Studies were under assumed the planning and assessment of solid dispersion of montelukast so as to develop fast release formulation of montelukast. In the preparation of solid dispersion conveys, for example, PEG what's more, HPMC were utilized. In this current investigation solid dispersion were arranged by solvent evaporation and fusion techniques. The solid dispersion arranged were Interaction to be fine and free streaming powders. Collaboration considers like IR spectra were appeared and there was no connection among medication and carriers utilized. All the solid dispersion arranged were seen as uniform in drug content. X-beam diffraction considers uncovered that crystalline nature of montelukast in unadulterated structure was diminished in the solid dispersion. This may be the purpose behind improved dissolution

## REFERENCES

1. Fincher, J.H.,1968. The Effect Of The Particle Size Of Drugs On Their Dissolution Rates And Biological Availability. J. Pharma. Sci. 57,1825.

2. Sekiguchi, K., Obi, N., 1961. New Solid state dispersions for

increasing dissolution rate. Chem. Pharm. Bull. 29, 899-867.

3. Goldberg, A.H., Gibaldi, M., Kanim, J.L., 1966. Increasing dissolution rates and gastrointestinal absorption of drugs via solid dispersions and eutectic mixtures III. Experimental evaluation of eutectic mixture: urea-acetaminophen system.J. Pharm. Sci. 55, 487-492.

4. Majerson M., Gibaldi M., 1966. New method of solid state

dispersion for increasing dissolution rates. J. Pharm. Sci. 13231324.

5. Ansel, H.C., Popovich, N.G., 1990. Pharmaceutical Dosage

Forms and Drug Deliveery System. Lea and Febiger, Philadelphia, PA, pp.1-50.

6. Ashimada, K., 1988. Polymorphic differences of α- nad ß-form crystala of some diones by X-ray diffraction infrared spectroscopy and differential scanning calorimetry. J. Pharm. Sci. 77(7), 635-637.

7. Bloch, D.W., Speicer, P., 1971. Solid dispersion fundamentals and examples. J. Pharm. Sci. 60(9), 1281-1302.

8. Chiou, W.I., Riegelman, S.J., 1971. Pharmaceutical applications of solid siapersios system. J. Pham. Sci. 60(9),1281-1302.

9. Donerty, C., York, P., 1989. Accelerated stability of an X-ray amorphous Furosemide-PVP solid dispersion. Drug Dev. Ind. Pharm. 15 (12), 1969-1987.

10. British Pharmacopoeia, (2003). vol.1. 874-875.