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# SOLUBILITY ENHANCEMENT OF BOSENTAN MONOHYDRATE BY USING HOT MELT EXTRUSION TECHNIQUE

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**ABSTRACT**

The aim of this study was to improve the solubility of bosentan monohydrate; a water insoluble drug belongs to BCS class II. Hot melt extrusion was applied to develop bosentan amorphous solid dispersions. Hot-melt extrusion can enhance drug solubility by stabilizing drug in amorphous form, deaggregating drug particles in a carrier and improving wettability of drugs. A poorly water-soluble drug and a hydrophilic polymer to a solid dispersion using hot-melt extruder. The mixture is extruded to a drug product. An increase in the drug solubility is obtained. A Solid dispersion based on soluplus and kollidon VA 64 was successfully prepared. Solubility of bosentan monohydrate solid dispersion was dramatically increased when compared with the bosentan monohydrate active pharmaceutical ingredient.

## INTRODUCTION:

Low aqueous solubility of API is a problem of drug product development. There are several methods to enhance drug solubility. Although drugs can increase solubility using many chemical and physical modifications, the few methods are able to enhance drug solubility for industrial scale. Hot-melt extrusion is one reliable process for enhancing drug solubility in a large scale production.

Hot-melt extrusion (HME) is one of the most widely applied processing technologies in the plastic, rubber and food industry. Interest in the pharmaceutical applications is growing rapidly and is evident from the increasing number of patents and publications. Limitations related to bioavailability and site specific drug delivery can be overcome by this technique. This technology has gained focus because of its ease of operation and fast processing.

Melt extrusion is considered to be an efficient technology with particular advantages over solvent processes like co-precipitation for the manufacture of a variety of dosage forms and formulations such as granules, pellets, tablets, suppositories, implants, stents, transdermal systems and ophthalmic inserts. The types of extruders currently available for hot melt extrusion are single and twin-screw extruders. Depending on the geometric design and function, the screw is generally composed of three different zones: feeding zone, melting zone, and the metering zone. HME also includes of its advantages, applications of hot melt extrusion technology and the optimization of HME process through which product quality and performance is assured.

Bosentan belongs to the class of organic compounds known as bipyrimidines and oligopyrimidines. These are organic compounds

containing two or more pyrimidine rings directly linked to each other. Pyrimidine is a 6-membered ring consisting of four carbon atoms and two nitrogen centers at the 1- and 3- ring positions Bosentan belongs to a class of drugs known as endothelin receptor antagonists (ERAs). Patients with PAH have elevated levels of endothelin, a potent blood vessel constrictor, in their plasma and lung tissue. Bosentan blocks the binding of endothelin to its receptors, thereby negating endothelin's deleterious effects. Bosentan is metabolized in the liver by the cytochrome P450 enzymes CYP2C9 and CYP3A4 (and possibly CYP2C19), producing three metabolites, one of which, Ro 48-5033, is pharmacologically active and may contribute 10 to 20% to the total activity of the parent compound. Poorly soluble in water (1.0 mg/100 ml) and in aqueous solutions at low pH (0.1 mg/100 ml at pH 1.1 and 4.0; 0.2 mg/100 ml at pH 5.0). Solubility increases at higher pH values (43 mg/100 ml at pH 7.5).

The solid-dispersion system is a well-established method for increasing the solubility of poorly water-soluble drugs. Several solid-dispersion methods such as the melting method, the solvent-evaporation method and the solvent-wetting method were previously reported to prepare the solid dispersions. Moreover, a novel solid-dispersion system termed 'surface-attached solid dispersion' has been developed. Unlike other solid dispersions, surface-attached solid dispersion is prepared with water and carriers without an organic solvent for enhancing the solubility and stability of poorly water soluble drugs. This solid-dispersion method has several advantages over other methods on an industrial scale, such as there being no necessity to remove an organic solvent, less potential toxicity and no danger of explosion of organic solvents. Furthermore, this solid dispersion could enhance the solubility and bioavailability of poorly water-soluble drugs without changing their crystalline state.

The main of the objective of this study, to evaluate the effect of the solid-dispersion fabricated using hot melt extrusion method on the solubility of poorly water soluble bosentan. Solid dispersions of bosentan with different ratios of polymers were fabricated and evaluated for solubility enhancement study, the polymers used for fabrication of solid dispersion are soluplus and kollidon VA 64. The solubility of drug in this solid dispersions were evaluated compared to drug powder solubility.

**Materials and Methods**

Bosentan is the free sample provided by Matrix API team. The polymers used in the hot melt extrusion process soluplus and kollidon VA 64 was the free samples provided by BASF. The active pharmaceutical ingredient and the polymers used in the manufacturing of the solid dispersion are of standard quality complying to official monographs. All the chemicals used for the analysis are laboratory grade complying to official standards.

**Experimental:**

**U.V method development for estimation of Bosentan solid dispersion**

**(a) Preparation of different reagents:**

**0.2 M Hydrochloric acid:** Took 17 mL of hydrochloric acid and diluted it with water up to 1000 mL

**2N Acetic acid:** Added 116 mL of glacial acetic acid to sufficient water to make 1000 mL after cooling to room temperature.

**0.2 M Monobasic Potassium Phosphate:** Dissolved 27.22 g of monobasic potassium phosphate ($KH_2PO_4$) in water, and diluted with water up to 1000 mL.

**0.2 M Potassium Chloride:** Dissolved 14.91 g of potassium chloride (KCl) in water, and diluted it with water up to 1000 mL.

**1% SLS in water:** Dissolved 1gm of sodium lauryl sulfate in 100 ml of water.

**(b) Preparation of different buffer media:**

pH 1.2 buffer**:** 85 ml of 0.2 M HCl was added to 50 ml of 0.2 M potassium chloride solution and volume was made up to 200 ml.

***Acetate Buffer p*H 4.5:** 2.99g of sodium acetate tri-hydrate ($NaC_2H_3O_2 \cdot 3H_2O$) was placed in a 1000-mL volumetric flask, transferred 14 ml of the 2N acetic acid solution into it, then added water to make up the volume and mixed well.

**Phosphate Buffer pH 6.8 and 7.4**: 50 ml of 0.2M monobasic potassium phosphate solution was taken in a 200 ml volumetric flask, to this added 22.4 and 39.1 ml of 0.2M sodium hydroxide solution and volume made up to 200 ml to get the respective pH.

**(c) Estimation of Drug in different medium by UV Spectrophotometer:**

**Standard Stock** – 100 mg equivalent drug was taken and added to respective media in a 100 ml volumetric flask and volume was made up to 100 ml, resulting in a standard stock solution of 1 mg/ml.

**Working Stock**–From the above standard stock solution 10 ml was taken and added to respective buffer media in a 100 ml volumetric flask and volume was made up to 100 ml. Two working stocks were prepared such that they can be used for preparation of samples in 6 replicates (3 similar concentrations from each working stock).

**(d) Determination of absorption maxima:**

10 µg/ml solution was taken to determine absorption maxima. Initially blank buffer solution was kept and scanned in the region of 200-400 nm. Then sample was kept for analysis and scanned in the same region. Absorption maxima were found to be 221 nm. Hence all further analysis was carried out at 221 nm for $P^H$ 1.2, $P^H$ 6.8, $P^H$ 7.4 buffers and water, 0.5% SLS in water,1% SLS in water.

**(e) Determination of Beer's law range and plotting of calibration curve**:

From the working stock solution 0.2, 0.4, 0.6, 0.8, 1 , 1.2 ml of sample was taken and diluted up to 10 ml using respective buffer media in a 10 ml volumetric flask resulting in concentrations of 2,4,6,8,10, and 12 µg/ml solutions. These were analyzed at 221 nm and calibration curve was plotted taking concentration in µg/ml on X-axis and absorbance units on Y-axis.

**Solubility**:

The solubility of drug is an important physicochemical property because it affects the bioavailability of the drug, the rate of drug release into dissolution medium Saturation solubility studies were performed by adding known excess quantity of drug in 100 ml of pH 2.0 hydrochloric acid buffer and buffers of different physiological pH (pH 1.2, pH 4.5, pH 6.8, pH 7.4 & water) and subjected to incubated shaking at 100 rpm for 24hrs at 36 $^0$C. The resultant super saturated solutions were collected and filtered through 0.45µ membrane filters and the concentration of drug was determined spectrophotometrically at a $\lambda_{max}$ of 221 nm.

**Preparation of Bosentan Solid Dispersion:**

**Preparation of Solid Dispersion by Hot-melt extrusion Technique:**

The carriers used in the study were soluplus and kollidon VA64 in the preparation of solid dispersion by hot melt extrusion method. Solid dispersions were prepared in bosentan : soluplus and bosentan : kollidon VA64 with ratio 1:1, 1:2, 1:3, 1:4 . Bosentan is initially mixed with soluplus and kollidon VA64 separately. The following temperatures were maintained in hot melt extruder during the extrusion process.

**Extrusion parameters of Solid dispersions:**

The drug and carrier blend was added to the feeding zone slowly. The formed extrudes were collected and milled through 40G screen using Quadracomill. The milled material was passed through sieve no. 60 (ASTM). The obtained solid dispersions were characterized for Solubility studies.

## CONCLUSION:

The main objective of this study was to enhance the aqueous solubility of bosentan monohydrate using hot-melt extrusion technique. Solid dispersion technique can be combined with traditional dosage forms such as tablets, capsules and pellets. From the results, it was observed that 16-20 folds at higher pH (6.8 & 7.4 pH) and 4-8 folds at lower pH (1.2) increased the solubility of bosentan monohydrate after preparing solid dispersion. Hence forth, it can be concluded that the of the drug solubility was enhanced by preparing Solid dispersion employing hot-melt extrusion technique, which resulted in enhanced solubility and dissolution rate of the drug and it can be assessed further bioavailability may also enhanced.

## ACKNOWLEDGMENT

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**Table No 1 : Composition of Bosentan solid dispersions**

| Formulation code | Composition of Solid Dispersions | Drug : Polymer Ratio |
|---|---|---|
| SD1 | Bosentan : Soluplus | 1:1 |
| SD2 | Bosentan : Soluplus | 1:2 |
| SD3 | Bosentan : Soluplus | 1:3 |
| SD4 | Bosentan : Soluplus | 1:4 |
| SD5 | Bosentan :Kollidon VA64 | 1:1 |
| SD6 | Bosentan :Kollidon VA64 | 1:2 |
| SD7 | Bosentan :Kollidon VA64 | 1:3 |
| SD8 | Bosentan :Kollidon VA64 | 1:4 |

**Table No 2: Hot Melt Extruder - Processing Parameters**

| S.No | Formulation | Temperature in different zones ($^{o}$C) | | | | Screw Speed (rpm) |
|---|---|---|---|---|---|---|
| | | Zone 1 | Zone 2 | Zone 3 | Zone 4 | |
| 1 | SD1 | 70 | 80 | 90 | 100 | 100 |
| 2 | SD2 | 70 | 80 | 90 | 100 | 100 |
| 3 | SD3 | 70 | 80 | 90 | 100 | 100 |
| 4 | SD4 | 70 | 80 | 90 | 100 | 100 |
| 5 | SD5 | 70 | 80 | 90 | 100 | 100 |
| 6 | SD6 | 70 | 80 | 90 | 100 | 100 |
| 7 | SD7 | 70 | 80 | 90 | 100 | 100 |
| 8 | SD8 | 70 | 80 | 90 | 100 | 100 |

**Table No 3: Solubility terminologies**

| S.No. | Descriptive term (solubility definition) | Parts of solvent required for one part of solute | Solubility range(mg/ml) | Solubility assigned(mg/ml) |
|---|---|---|---|---|
| 1 | Very soluble | <1 | ≥ 1000 | 1000.00 |
| 2 | Freely soluble | From 1 to 10 | 100-1000 | 100.00 |
| 3 | Soluble | From 10 to 30 | 33-100 | 33.00 |
| 4 | Sparingly soluble | From 30 to 300 | 10-33 | 10.00 |
| 5 | Slightly soluble | From 100 to 1000 | 1-10 | 1.00 |
| 6 | Very slightly soluble | From 1000 to 10000 | 0.1-1 | 0.10 |
| 7 | Practically insoluble | ≥ 10000 | < 0.1 | 0.01 |

**Table No 4: Table showing solubility studies of drug in different buffers**

| S.NO. | Medium | Solubility(mg/ml) |
|---|---|---|
| 1. | Water | 0.012 |
| 2. | pH 1.2 | 0.01 |
| 3. | pH 4.5 Acetate buffer | 0.034 |
| 4. | pH 6.8 Phosphate buffer | 0.36 |
| 5. | pH 7.4 Phosphate buffer | 0.42 |

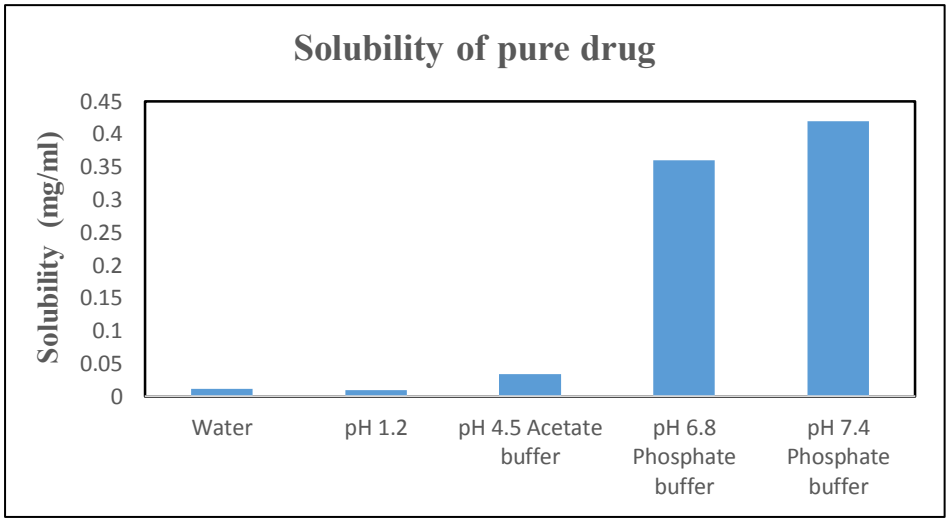


**Fig 1: showing solubility studies of drug in different buffers**

**Inference**: As per USP Definition, The solubility data indicates that the drug is practically insoluble in water and very slightly soluble in higher pH (6.8 and 7.4). It indicates the drug had pH dependent solubility.

**Table No 5: Solubility studies of solid dispersions at different pH conditions**

| Solubility in mg/ml | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **pH** | **SD1** | **SD2** | **SD3** | **SD4** | **SD5** | **SD6** | **SD7** | **SD8** |
| 1.2 | 0.63 | 0.83 | 0.56 | 0.36 | 0.41 | 0.482 | 0.39 | 0.23 |
| 4.5 | 0.83 | 1.13 | 1.06 | 0.96 | 0.91 | 0.82 | 0.69 | 0.63 |
| 6.8 | 5.64 | 8.38 | 6.02 | 5.92 | 6.46 | 4.49 | 2.98 | 2.16 |
| Water | 1.08 | 1.86 | 1.64 | 1.32 | 1.18 | 1.68 | 1.25 | 1.13 |
| 7.4 | 6.14 | 8.99 | 6.94 | 5.23 | 5.16 | 4.95 | 3.1 | 1.96 |

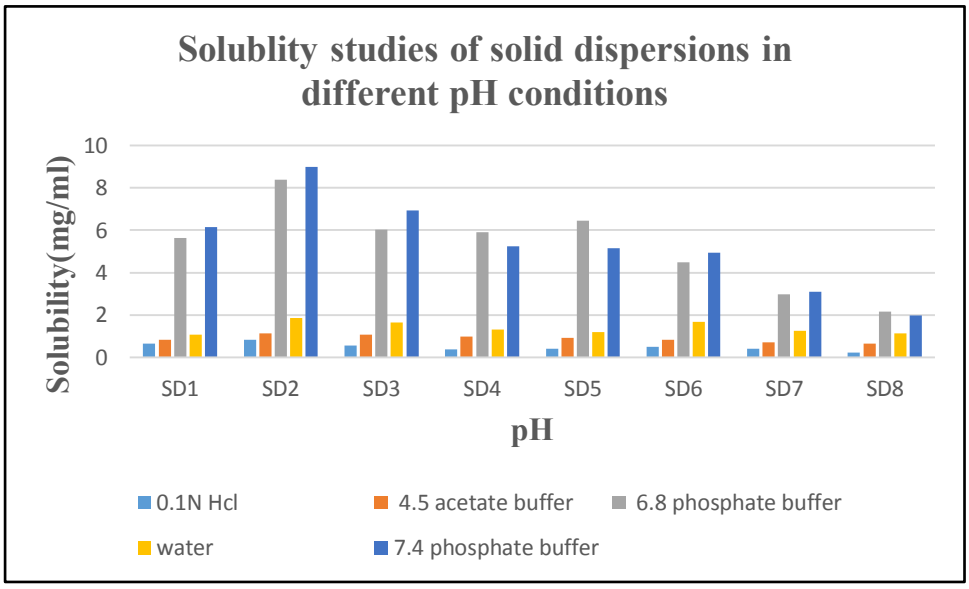


**Fig 2: solubility studies of solid dispersions in different pH conditions**

**Inference**: from the above data, 16-20 folds at higher pH (6.8 & 7.4 pH) and 4-8 folds at lower pH (1.2) increased the solubility of model drug after preparing solid dispersion. Hence, SD2 solid dispersion was considered for further evaluation.

**REFERENCES**


1. Jung Hyun Joe, Won Mo Lee, Effect of the solid-dispersion method on the solubility and crystalline property of tacrolimus, International Journal of Pharmaceutics 395 (2010) 161–166
2. Sachin, hot-melt extrusion, Int. J. Pharm. Sci. Rev. Res., 15(1), 2012; nº 21, 105-112
3. Bhavesh B. Patel, Revealing facts behind spray dried solid dispersion technology used for solubility enhancement, Saudi Pharmaceutical Journal (2015) 23, 352–365
4. Sandeep Kalepua, Vijaykumar Nekkanti, Insoluble drug delivery strategies: review of recent advances and business prospects, Acta Pharmaceutica Sinica B
5. Michael Linn, Eva-Maria Collnot, soluplus as an effective absorption enhancer of poorly soluble drugs in vitro and in vivo, European Journal of Pharmaceutical Sciences 45 (2012) 336–343.
6. Yan he, chris ho, Amorphous solid dispersions: utilization and challenges in drug discovery and development, *Journal of pharmaceutical sciences* 104:3237–3258, 2015.
7. www.drugbank.ca
8. Smita Kolhe, Dr. Praveen Chaudhari, Dhananjay More "Dissolution Enhancement of Poorly Water Soluble Efavirenz by Hot Melt Extrusion Technique" Int. J. Drug Dev. & Res., April-June 2013, 5(2): 368-381
9. Sanjeevani Desai, John disouza, Kiran musle, Hoshmani Avinash, solubility enhancement of ritonavir by hot melt extrusion, vol 8, issue 3, 2016
10. Breitenbach J. Melt extrusion: from process to drug delivery technology. Eur J Pharm Biopharm 2002; 54:107-17.
11. Repka MA, Battu SK. Pharmaceutical application of hot melt extrusion part: part–I. Drug Dev Ind Pharm 2007; 33:909-26.
12. Choudhary D, Kumar S, Gupta GD. Enhancement of solubility and dissolution of Glipizide by solid dispersion (kneading) technique. Asian J Pharm Sci 2009; 3:245-51.