

Dissolution Enhancement of Domperidone Fast Disintegrating Tablet Using Modified Locust Bean Gum by Solid Dispersion Technique

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Abstract Enhancement of dissolution characteristics of poorly soluble drug Domperidone by solid dispersion technique using modified locust bean gum (MLBG) and further conversion into tablet dosage form with fast dissolving characteristics is being explored in current study. Solid dispersions (SD) were prepared by solvent evaporation technique. F1, F3, F5 and F7 batches of SD (1:1, 1:3, 1:5 and 1:7 ratio of drug to MLBG) were prepared. Maximum solubility was observed in 1:3 ratio (F3 batch) in comparison to pure drug. Fourier Transform Infrared spectroscopy studies revealed no interaction of drug to polymer MLBG. Transition from crystalline to amorphous state of drug was analyzed by X-RD studies. SEM studies revealed change in surface characteristics of drug in solid dispersions. In vitro release studies revealed maximum dissolution in F3 (93% in 30 min). Further solid dispersion batches F3 was compressed into tablets including other excipients and crosspovidone as superdisintegrant. The *in vitro* release from tablet batch revealed better dissolution characteristics (95% in 30 min) in comparison to marketed tablet (50% in 60 min). Therefore, MLBG solid dispersion tablets of domperidone can be a convenient dosage form with enhanced dissolution characteristics.

Keywords: Solubility, Natural carrier, Dissolution, Solid dispersions, Disintegration

1. INTRODUCTION

Recent drug development in pharmaceutical industry emphasizes on use of modified polymers or novel excipients for improved oral bioavailability of

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BCS Class II drugs (poor solubility and good permeability). Various techniques have been evidenced to enhance the solubility of poorly soluble drugs such as micronization, salt formation, liquid solids compacts, complexation with polymers, prodrugs, co-precipitation using antisolvent, pH alteration, use of surfactants, and solid dispersions. Solid dispersion has been widely employed technique to improve the dissolution characteristics of poorly soluble drugs. The solid dispersion has been defined as a dispersion of one or more API (active pharmaceutical ingredient) in an inert carrier or matrix at the solid state prepared by solvent-melting method. Solid dispersion is practically simple technique which can overcome the limitations of the above techniques (8, 7). Domperidone maleate (DOM), an antiemetic drug, has poor aqueous solubility and high permeability (BCS class II drug). It is slightly soluble in water (0.0925mg/mL) and has low oral bioavailability (13-17%). It shows high protein binding (91-93%) (<http://www.drugbank.ca/drugs/DB01184>). Research reports have mentioned improved solubility of Domperidone by solid dispersion technique using different carriers (PVP K30 and Poloxamer 188 and PEG 6000; sodium alginate etc) (2, 6). Fast dissolving tablets have been reported using Domperidone binary and ternary solid dispersions containing (Gelucire 44/14 and Gelucire 50/13; Poloxamer 188 and 407; PEG 6000, 4000 and PVP K30) and also of HP β -CD inclusion complex of Domperidone) (5, 11). The use of MLBG has now been widespread being a natural carrier with a number of poorly soluble drugs for solubility enhancement (Atorvastatin, Glibenclamide etc) (4, 9).

Current study employed solid dispersions technique using modified locust bean gum for development of fast disintegrating tablets of domperidone.

2. MATERIALS AND METHODS

2.1 Materials

Pure drug Domperidone was kindly gifted by IPZAH Pharmaceuticals Ltd, Patiala; Locust Bean Gum was gifted by Lucid Colloids Ltd, Delhi. Other chemicals used were of AR grade.

2.2 Methods

2.2.1 Preparation of Solid Dispersions

Solid dispersions of Domperidone (drug substance) were prepared by using MLBG via solvent evaporation method. Pure drug and polymer MLBG was dissolved/dispersed in ethanol (25 ml) in round bottom flask and dispersions were prepared using rotary evaporator at 45-50°C under vacuum. The four

batches (F1, F3, F5 and F7) were prepared in different drug to polymer ratios (1:1, 1:3, 1:5 and 1:7). All the formulations were first analyzed for solubility studies.

2.2.2 Evaluation of Solid Dispersions

Equilibrium Solubility Studies

The equilibrium solubility of solid dispersions was determined in distilled water at 37°C. For each preparation, an equivalent of 10 mg of drug was added to 50 ml of distilled water in conical flasks. The flasks were kept in shaking incubator for 24 h at 37±0.5°C. Then, the solution was filtered and the filtrate was assayed spectrophotometrically at 284nm.

Fourier Transform Infrared Spectroscopy

About 10 mg of the sample was mixed with dried potassium bromide of equal weight. The mixture was properly grinded using pestle and mortar. Pellets are formed by compressing the mixture by using hydraulic press. Transparent pellets formed in this way are scanned. The spectra are scanned over a frequency range 4000 – 500 cm⁻¹. Infrared absorption spectra of Domperidone (drug substance) and solid dispersion batch F3 was obtained using potassium bromide disks, under static air using FTIR spectrophotometer.

Scanning Electron Microscopy (SEM)

Samples of Domperidone (drug substance), best batch of solid dispersions (F3) were mounted onto the stubs using double sided adhesive tape and then coated with gold palladium alloy (150-200 Å) using fine coat ion sputter (JEOL, fine coat ion sputter, JSM-6100, USA). The samples were subsequently analyzed under the scanning electron microscope for external morphology.

X-Ray Diffraction (X-RD)

Powder X-Ray diffraction patterns were traced employing X-ray diffractometer (X'PertPro, India) for the samples using Ni filtered Cu (K-α) radiations, a voltage of 45 kV, a current of 40 mA. The samples were analyzed over 2θ range of 0-50° with scan step size of 0.0170° (2θ) and scan step time 25 s.

2.3 Conversion into Tablet Dosage Form

The best batch of solid dispersion (F3) was compressed into tablets (200mg) by adding various excipients (Avicel 112, mannitol, talc and magnesium stearate). Crosspovidone (CP) was also added to enhance the disintegration characteristics. The tablet formulation batches (with and without CP) were evaluated further. The composition of tablet batches is given in Table 1.

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Table 1: Composition of tablet batches.

| Ingredients | T1(mg) | T2(mg) |
|------------------------------------|---------------|---------------|
| SD powder(eq. to 10 mg drug) | 40 | 40 |
| Avicel 112 | 120 | 110 |
| Mannitol | 35 | 35 |
| Talc | 2 | 2 |
| Magnesium Stearate | 3 | 3 |
| Crosspovidone (CP) | – | 10 |
| Total weight of tablet (mg) | 200 | 200 |

2.4 Physicochemical Characterization of Tablets

All the standard tests for tablets (weight variation, friability, hardness and disintegration) were done as specified in reference standards. Other tests such as water absorption ratio and wetting time were carried out as reported in literature.

Wetting Time

Five circular tissue papers of 10cm diameter were placed in a petridish (10cm diameter). 10 mL of water containing Eosin, a water soluble dye, was added to petridish. A tablet was carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as wetting time (1, 10).

Water Absorption Ratio

A piece of tissue paper folded twice was placed in a small Petri dish (6mm) diameter containing 6 ml of water. A tablet was put on the paper & the time required for complete wetting was measured (1, 10). The wetted tablet was then weighed. Water absorption ratio, R, was determined using following equation.

$$R=100(W_a/W_b)$$

Where, W_b is weight of tablet before water absorption and W_a is weight of tablet after water absorption.

2.5 *In vitro* Dissolution Studies

In vitro dissolution of tablet batch T2, various solid dispersions and marketed tablet T3 was carried out in 900 mL of 0.1N HCl at $37\pm 0.5^\circ\text{C}$ with the stirrer rotation speed of 50 rpm using USP II dissolution apparatus. 5ml aliquots were

withdrawn at regular intervals of 5, 15, 30, 45, 60, 120 min and suitably diluted and assayed spectrophotometrically at 284 nm.

3. RESULTS AND DISCUSSION

3.1 Equilibrium Solubility Studies

Equilibrium solubility of Domperidone (drug substance) in distilled water was found to be very low i.e. 2.96 ($\mu\text{g/ml}$). Mixing of drug with MLBG in solid dispersions (F1, F3, F5 and F7) leads to increase in solubility of drug which may be due to wetting characteristics of MLBG. However the higher ratio of polymer MLBG (F5, F7) showed a decrease in the equilibrium solubility. MLBG in higher ratio caused increased viscosity of the mixture which hinders drug solubilization and thereby dissolution also. The comparative solubility data is given in Table 2 and shown in Figure 1.

Table 2: Equilibrium solubility data of solid dispersion batches.

| Formulation | Solubility value ($\mu\text{g/ml}$) |
|----------------|---------------------------------------|
| Pure Drug (PD) | 2.837838 |
| F1 | 21.3964 |
| F3 | 35.74324 |
| F5 | 28.24324 |
| F7 | 23.35586 |

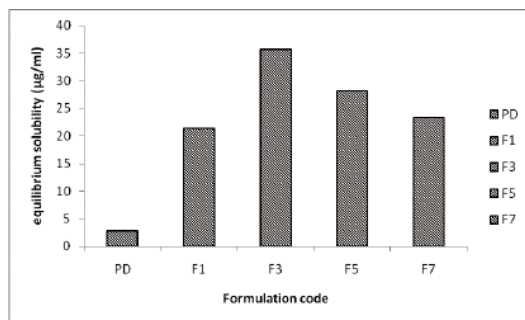


Figure 1: Equilibrium solubility of pure drug (PD) Domperidone and various solid dispersions (F1, F3, F5 and F7).

3.2 Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra were traced to establish the presence of different functional groups. FTIR spectra of Domperidone and solid dispersion batch F3 is shown in Figure 2 and 3. FTIR spectrum of sharp characteristic bands at 3125.18, 1694, 1486.33, 1382.68 and 1150 cm^{-1} due to stretching vibration bands of C=O, N-H, C-N, and two C-O respectively. The presence of almost all characteristic peaks of drug (3025.41, 1690.87, 1462, 1374.86 and 1150.43 cm^{-1}) in spectra of solid dispersion batch (SD3 batch) indicated no interaction of drug with polymer.

3.3 Scanning Electron Microscopy

Scanning electron micrographs of the Domperidone (drug substance) and solid dispersion batch F3 shown in Figure 4a and 4b respectively. The drug appeared

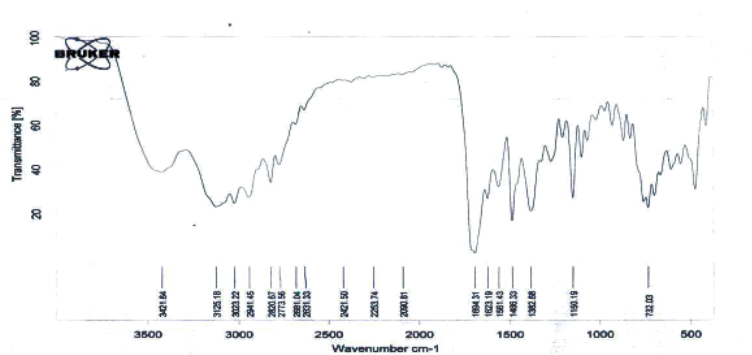


Figure 2: FTIR spectrum of pure drug domperidone.

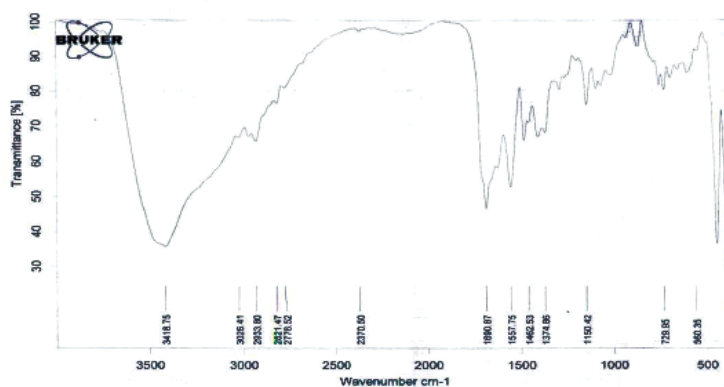


Figure 3: FTIR spectrum of solid dispersion batch F3.

as crystalline particles while porous surfaced particles were observed in solid dispersion batch (F3) indicating changes in crystallinity of drug.

3.4 X-Ray Diffraction

The crystallinity characteristics of Domperidone (drug substance) and polymer MLBG was determined by X-ray diffraction studies by comparing some characteristic peak heights in the diffraction pattern of the formulations with that of pure drug. The X-RD pattern of drug, solid dispersion F3 batch and MLBG are shown in overlay diagram (Figure 5). Domperidone showed sharp peaks of the diffraction angle of 2θ at 14.32, 15.81, 19.96 and 24.97 with peak

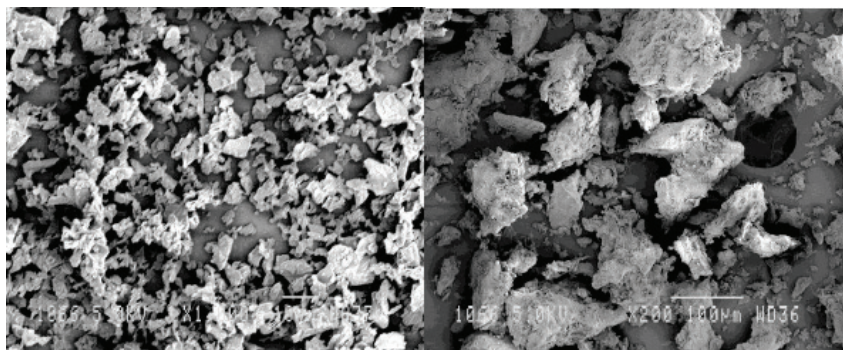


Figure 4: SEM image of a) pure drug domperidone b) solid dispersion batch F3.

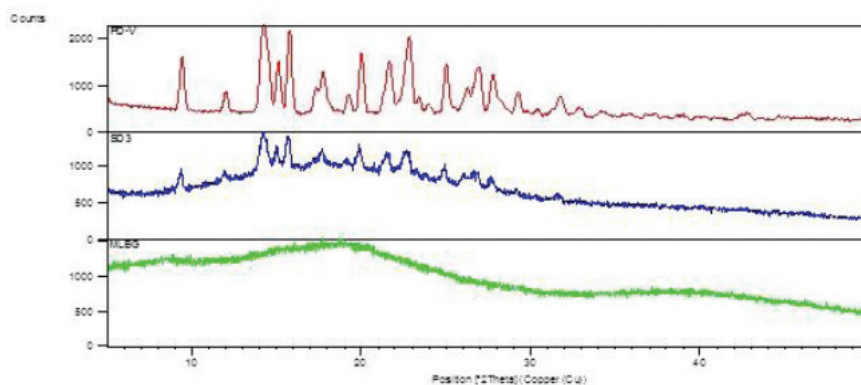


Figure 5: Overlay diagram of X-RD of pure drug Domperidone, F3 solid dispersion and MLBG.

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intensities of 100, 95.02, 69.04 and 57.00 respectively; and the area of 297.56, 565.48 and 339.21 respectively. Characteristic peaks of drug with decreased intensity were observed in diffraction patterns of solid dispersion batch SD3. The X-RD results revealed partial conversion from crystalline to amorphous form of drug in the solid dispersion.

3.5 Conversion into Tablet Dosage Form

Tablets were compressed of solid dispersion batch F3. Two batches of tablets containing F3 solid dispersion powder (T1 and T2 with and without crosspovidone respectively). T1 tablet batch shows slight chipping during compression which was overcome by adding crosspovidone (T2 batch). Therefore only T2 batch was further evaluated and further compared with marketed tablet (Vomistop, Cipla). Marketed tablet was coded as T3.

3.6 Physicochemical Characterization of Tablets

T2 tablet batch was evaluated for various standard tests (weight variation, hardness, and friability, disintegration, wetting time, water absorption ratio and in vitro drug release). The results are depicted in Table 3. % weight variation of all tablets was within pharmacopoeial limits ($\pm 7.5\%$). The prepared tablets possessed sufficient hardness in the range (between 3-3.5 kg/cm²) as indicated by good mechanical strength. The good mechanical resistance is shown by friability values below 1% for the tablet batch. The wetting time and disintegration time values of less than 1 min were observed in tablet batch T2. Water absorption ratio of more than 100% in T2 batch suggested sufficient swelling and disintegration of tablet leading to better dissolution characteristics.

Table 3: Physicochemical parameters of tablet batch T2 and marketed tablet.

| Parameters | Tablet (T2) | Marketed tablet (Vomistop) T3 |
|--------------------------------|-----------------|-------------------------------|
| Weight variation (mg) | 196.84 | 198.34 |
| Hardness (kg/cm ²) | 2.7 \pm 0.4 | 3.5 \pm 0.3 |
| Friability (%) | 0.75 \pm 0.05 | 0.54 \pm 0.04 |
| Disintegration Time (sec) | 26.5 \pm 3 | 165 \pm 5 |
| Wetting Time (sec) | 24 \pm 2 | 172 \pm 6 |
| Water absorption ratio (%) | 117.45 | 86.87 |

Marketed tablet T3 passed all the tests (results were in pharmacopoeial limits as for conventional tablets).

3.7 *In vitro* Dissolution studies

In vitro release from various solid dispersions using MLBG (F1, F3, F5 and F7) is shown in Figure 6. Maximum dissolution characteristics were observed in SD batch F3 with (70% in 15 min and 100% release in 45min). The results were also in confirmation with solubility data. The drug release was decreased in F5 and F7 which may be due to the reason that higher ratio of polymer lead to viscous mixtures which further hinders the drug dissolution. The improved dissolution of solid dispersions may be due to increase in wettability, decrease in particle size of drug and reduced crystallinity of drug. The decreased viscosity of MLBG led to use of gum in higher ratio in the formulation which otherwise may not be possible with LBG.

The drug release from tablet batch T2 was compared with marketed tablet T3 (Figure 7). Tablet batch T2 showed 100% release in 45 min which is significantly higher than that of marketed tablet T3 (45% in 60 min). The results also revealed that compression into tablet does not significantly affect the release characteristics which were comparable with that of F3 solid dispersion. The presence of croscopolvidone may lead to better disintegration and thereby dissolution.

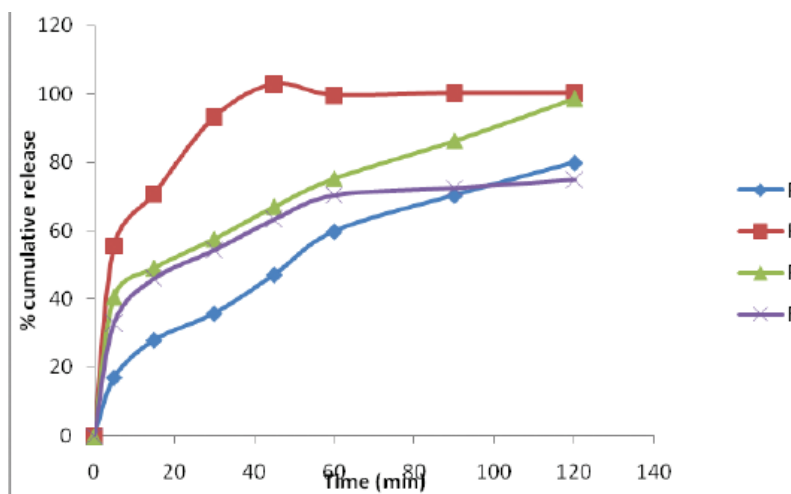


Figure 6: Comparative *in vitro* release of various solid dispersions (F1, F3, F5 and F7).

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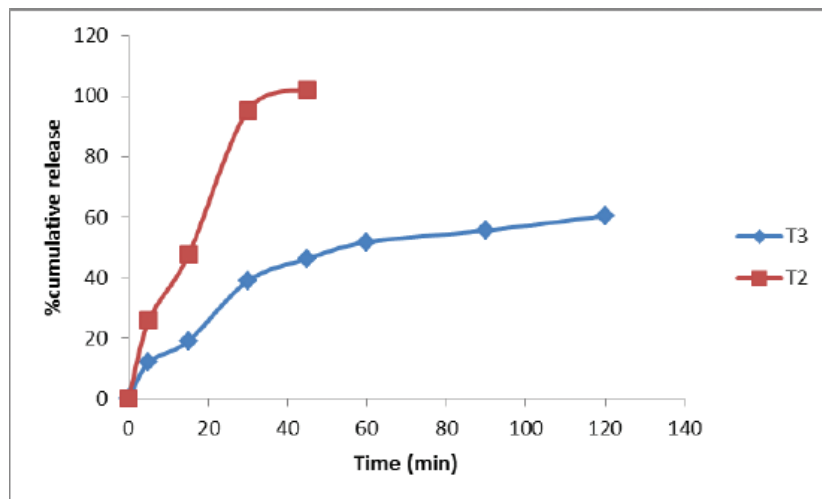


Figure 7: Comparative in vitro release of tablet batch T2 and marketed tablet (vomistop) T3.

CONCLUSION

The potential of natural carrier MLBG is being explored for the solubility enhancement of Domperidone fast dissolving tablets. The wetting ability of MLBG alongwith reduced particle size of the drug in solid dispersions led to improved dissolution of drug. The improved dissolution characteristics of solid dispersion powder of drug in fast dissolving tablets further results in enhanced bioavailability of drug in comparison to that of pure Domperidone fast dispersible tablets.

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