Dissolution Enhancement of Domperidone Using Water Soluble Carrier by Solid Dispersion Technology


ABSTRACT: Domperidone is a highly water insoluble drug exhibiting poor dissolution pattern. This is the cause for its poor absorption. Currently, several products of this drug substance is available in the market. Solid dispersions of domperidone were prepared using different ratios of polyvinylpyrrolidone as carrier by kneading method. They were evaluated for drug content, intactness of the drug in the formulation and dissolution. IR spectral and DSC studies were used to characterize the solid dispersion and to study the possibility of complexation of drug with carrier. The dissolution of domperidone from the solid dispersions exhibited higher rates of dissolution and dissolution efficiency values over that of pure drug.

KEYWORDS: Domperidone, polyvinylpyrrolidone, solid dispersions, kneading method and in vitro release.

Introduction
The therapeutic efficacy of a drug product intended to be administered by the oral route mainly depends on its absorption by the gastrointestinal tract. However, for a drug substance to be absorbed, it needs to be solubilised. Numerous works have been carried out in order to modify the dissolution kinetics of poorly soluble drugs to improve their bioavailability. Among them solid dispersion technology was most widely used (Sekiguchi et al., 1961, Chiu et al., 1971, Law et al., 1992, Corrigan, 1985, Craig, 1990 and Ford, 1986). Number of insoluble drugs has shown to improve their dissolution character when converted to solid dispersion (Madhusudhan et al., 2002). Solid dispersion technology is a well known process used to increase the dissolution kinetics and oral absorption of poorly water soluble drugs using water soluble inert carriers (Delahaye et al., 1997). The use of hydrophilic polymers as carriers for the dissolution enhancement of poorly water-soluble drug is increasing (Okimoto et al., 1997 and Yamada et al., 1999) Various hydrophilic carriers such as polyethylene glycol (Margaret et al., 1994), polyvinylpyrrolidone (Yagi et al., 1996) and sugars (Danjo et al., 1997) have been investigated for improvement of dissolution characteristics and bioavailability of poorly aqueous soluble drugs. Polyvinylpyrrolidone (PVP) has been used for the preparation of solid dispersion as a component of binary system for various drugs (Sheu et al., 1994). Domperidone, a D-2 antagonist used as antiemetic has poor aqueous solubility (0.986mg/L) and its oral bioavailability is only 13.17% (Barone, 1993). The present investigation aims to evaluate the potential of solid dispersion technique for domperidone using polyvinylpyrrolidone as hydrophilic carrier. Further, this study undertakes to investigate kneading as a technique for preparation of such binary systems, their solid state characterization and attempts to see the possible mechanism of improved dissolution rate.

Materials and Methods
Domperidone was obtained as a gift sample from M/s. Amananth Pharmaceuticals, Pondicherry, India. Polyvinylpyrrolidone (PVP K30) was procured from S.D. Fine chemicals, Mumbai. All other reagents and solvent used in the study were of analytical grade.

Phase Solubility Studies
Solubility requirements for domperidone were carried out by a reported method (Higuchi et al., 1965). An excess amount of domperidone (50mg) was added to the aqueous solution containing various concentrations of polyvinylpyrrolidone (0.05 to 0.25% wt/vol) in a series of 25 ml stoppered conical flask. The flasks were shaken for 24 hours at room temperature (28°C) on a rotary flask shaker. After 24 hours of shaking to achieve equilibrium, 5 ml of aliquots were withdrawn, filtered (0.45 μm pore size) and spectrophotometrically analyzed for drug content at 280 nm (Shimadzu-UV 160 A spectrophotometer) (figure 1).

Preparation of Solid Complexes by Kneading Method
(Aftab Modi et al., 2006)
A mixture of domperidone and polyvinylpyrrolidone in different ratios (1:1, 1:2, 1:3, 1:4 and 1:5 w/w) were wetted with methanol and kneaded thoroughly for 30 minutes in a glass mortar. The paste formed was dried under vaccum for 24 hours. Dried powder was scraped, pulverized and passed through sieve no 100 (ASTM-100, 150 μm) and stored in dessicator. The prepared solid dispersions were evaluated for its various physicochemical parameters such as yield, angle of repose, bulk density, compressibility, moisture uptake, drug content and in vitro dissolution studies. (Table 1)
Fourier Transform Infrared (FTIR) Spectroscopy

FTIR spectra were recorded on samples prepared by kneading method in different ratio’s of carrier (w/w) in a KBr pellets using Perkin Elmer FT/IR – 5300 (Tokyo, Japan). The scanning range was 450 to 4000 cm⁻¹ and the resolution was 4 cm⁻¹.

Differential Scanning Calorimetry (DSC)

DSC analysis was performed using Netzsch DSC 204, Tokyo, Japan. The samples were heated in a sealed aluminium pans at a rate of 10° C per min⁻¹ in a 30 to 300° C temperature under nitrogen flow of 40 mL/min.

Dissolution Rate Studies (Nagersankar et al., 2000)

*in vitro* dissolution rate studies were performed in phosphate buffer (pH 6.8) maintained at 37±0.5° C, using a 6 station USP XXII dissolution apparatus (TDT-50, Electrolab, Mumbai, India) with basket rotating at 50 rpm. Solid dispersions containing 100 mg of drug were subjected to dissolution. At fixed time intervals, samples were withdrawn, filtered and assayed for domperidone by measuring the absorbance at 280 nm (figure 2). Dissolution efficacy was calculated from the area under the dissolution curve at time ‘t’ (measured using the trapezoidal rule) and expressed as percentage of the area of the rectangle described by 100% dissolution in the same time (Khan, 1975).
Fig. 2 in vitro dissolution profiles of solid dispersion containing domperidone. Bulk drug (♦), DSD-I (●), DSD-II (▲), DSD-III (×), DSD-IV (●) and DSD-V (∆). Samples were withdrawn at different time intervals and domperidone was determined by UV spectrophotometer.

Results and Discussion

The phase solubility diagram for the complex formation between domperidone and polyvinylpyrrolidone is shown in figure 1. The aqueous solubility of domperidone is increased linearly (r = 0.9989) as a function of carrier concentration. The phase solubility diagram showed A_L type, due to the straight line had a slope less than unity; indicates the formation of complex. The apparent stability constant, K_c was calculated from the linear plot of the phase solubility diagram according to the equation.

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K_c = \frac{\text{Slope}}{S_0(1-\text{Slope})}
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Where, \( S_0 \) is the solubility of domperidone in the absence of PVP. The stability constant, \( K_c \) of domperidone PVP complex was found to be 199.78 M^{-1}, which indicates the formation of stable complex for A_L type solid complexes prepared by kneading method. The FTIR spectra of domperidone and its binary systems with PVP are presented in figures 3a, 3b and 3c. Pure drug showed sharp characteristic peaks at 3120, 1694 and 1384 cm^{-1}. All the above characteristic peaks appear in the spectra of binary systems at same wave number indicating no modification or interaction between drug and carrier.

Thermal behavior of pure drug and corresponding drug carrier systems are depicted in figures 4a, 4b and 4c. The DSC curve of domperidone profiles a sharp exothermic peak (T peak 248°C) corresponding to its melting point. However, the characteristic exothermic peak, corresponding to drug was broadened and shifted towards lower temperature, with reduced intensity in the solid dispersions. This could be due to the higher concentration and uniform distribution of drug in the crust of polymer, resulting in the complete miscibility of drug and carrier. Moreover, the data also indicates there seems to be no interaction between the components of binary systems. No significant difference in DSC pattern of dispersions suggest that even the kneading process could not induce the interaction at molecular level and the solid dispersion formed as highly dispersed drug crystals in carrier. Solid dispersions prepared by kneading method were found to be fine and free flowing in characteristics. The yield of solid dispersions was ranged from 84.17±1.1 to 98.99±0.5%. The bulk density, flow property and moisture uptake were found to be satisfactory. The bulk density values of solid dispersions ranged from 0.80 to 0.91 g/cc and the angle of repose for solid dispersion was found to be 23 to 25°. This may be
due to decrease in intraparticulate friction. The moisture uptake of solid dispersions was found to be in the range of 8 to 9%, and the compressibility of solid dispersions was ranging from 15 to 18%, respectively for the batches DSD-I to DSD-V. This may be helpful in filling and compressional process. The drug content of domperidone in solid dispersions was ranged from 95.11 to 98.13%. Dissolution profiles of pure drug and solid dispersions are presented in figure 2. It is evident that the solid dispersion technique has improved the dissolution rate of domperidone to a great extent. Table 1 summarizes dissolution efficiency at 50 minutes for domperidone and its binary systems with carriers. The enhancement of dissolution of domperidone from the drug carrier may be due to several factors such as lack of crystallinity, increased wettabiliy and dispersibility. Incorporation of drug with a hydrophilic carrier system offered an increased wetting and reduction in interfacial tension between hydrophobic drug and dissolution medium (Narender Reddy et al., 2004). It was observed during the dissolution studies that drug release from the solid dispersion was found to be faster. As the proportion of polyvinylpyrrolidone in solid dispersion increases, there was an increase in the dissolution rate of the drug. The solid dispersion prepared using 1:5 drug carrier ratios (DOM-V) achieved maximum dissolution rate of drug. The batch DOM-V showed 6.27 fold increases in the dissolution rate compared to pure drug. The 'k' values of solid dispersion were found to be more than pure drug followed first order kinetics (Gopal Rao et al., 2005).
The study shows that the dissolution rate of domperidone can be enhanced to a great extent by solid dispersion technique using an industrially feasible kneading method. The solid dispersion complex of drug was giving better dissolution profile as compared to pure drug. This in turn, can reduce the doses of drug, reduction in dose related adverse effects and improved bioavailability.

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References


