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Development of Domperidone Solid Dispersion Powders Using Sodium Alginate as Carrier

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Abstract: Domperidone is a widely used antiemetic, poorly water soluble drug, erratically absorbed in stomach and possess several dissolution-related problems thus it has poor bioavailability (13-17%). The rate and extent of dissolution of the drug from any solid dosage form determines the rate and extent of absorption of the drug. Several methods have been employed in order to improve the dissolution and bioavailability of sparingly soluble drugs. Among the various approaches, the solid dispersion technique has proved to be the most successful, simple and economic in improving the dissolution and bioavailability of poorly soluble drug. The aim of the present study was to investigate the possibility of improving the solubility and dissolution rate of a novel sodium alginate based solid dispersion of domperidone using fusion method, solvent evaporation method and solvent melt method. The prepared solid dispersions were characterized for their drug content, drug-carrier compatability and *in-vitro* dissolution study. All the formulation showed marked improvement in the solubility and dissolution rate of drug which may be due to hydrophilic polymers would improve the aqueous solubility, dissolution rate and thereby enhancing its systemic availability. It was concluded that sodium alginate is a suitable carrier in solid dispersion technique to improve the solubility and dissolution rate of the poorly soluble drug like domperidone.

Key words: Domperidone% · Sodium Alginate% · Solid Dispersion% · Bioavailability

INTRODUCTION

Domperidone, a dopamine D2 receptor antagonist, is used as a prokinetic and antiemetic agent for the treatment of gastroparesis, nausea and vomiting [1]. Domperidone is a weak base with good solubility in acidic pH but in alkaline pH, its solubility is significantly reduced [2] and it is poorly water soluble drug (log p, 3.1), has low absorbability after oral administration and undergoes extensive first pass metabolism [3-5]. The poor aqueous solubility may be one possible reason for its low bioavailability (13-17%). In addition, drug release is a critical and rate limiting step for oral drug bioavailability, particularly for drugs possessing low gastrointestinal solubility and high permeability [3, 6].

Oral bioavailability of drugs depends on its solubility and/or dissolution rate, therefore major problems associated with these drugs was its very low solubility in biological fluids, which results into poor bioavailability after oral administration [7-11]. The enhancement of oral bioavailability of poor water soluble drugs remains one of the most challenging aspects of drug development [12]. Together with the permeability, the solubility behaviour and the dissolution rate of a drug is a key determinant of its oral bioavailability and is one of the most important concerning aspects of the pharmaceutical industries [11, 13, 14].

Many methods are available to improve dissolution rate, solubility characteristics, including salt formation, micronization and addition of solvent or surface active agents. Solid dispersion (SDs) is one of these methods, which was most widely and successfully applied to improve the solubility, dissolution rates and consequently the bioavailability of poorly soluble drugs. The concept of solid dispersions (SDs) was introduced in 1961 by Sekiguchi and Obi [7], in which the drug is dispersed in inert water - soluble carrier at solid state. This technique has been used for a wide variety of poorly aqueous soluble drugs such as nimesulide [15], ketoprofen [16], tenoxicam [17], nifedipine [18], nimodipine [19].

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Various methods are used to prepare solid dispersion which includes solvent wetting method, physical mixture, solvent evaporation method, melting method, solvent wetting method, fusion method, kneading method and super critical fluid method etc [20-22].

The aim of the present study was to investigate the possibility of improving the solubility and dissolution rate of a novel sodium alginate based solid dispersion of domperidone using fusion method, solvent evaporation method and solvent melt method. The prepared solid dispersions were characterized for their drug content, drug-carrier compatibility and *in-vitro* dissolution study.

MATERIALS AND METHODS

Domperidone was purchased from the Torrent pharmaceuticals, Ahmadabad. Sodium alginate was purchased from the Sigma-Aldrich, Germany. Urea was purchased from the SD Fine Chemicals Ltd, Mumbai. All other chemicals were of analytical reagent grade.

Preparation of Solid Dispersions

Solvent Evaporation Method: The physical mixture of the drug and water soluble carrier is dissolved in a common solvent and the resulting clear solution is rapidly heated for evaporating the solvent and to get a glassy solid mass. Briefly, the sodium alginate polymer was dissolved in 20% ethanol under stirring, until a clear solution was obtained, domperidone was then added and stirring was continued for 45 min. The organic solvent was removed by evaporation on a water bath at 60°C. The resultant solid dispersions were stored in a desiccator until constant mass was obtained, pulverized and passed through sieve No. 22 [23].

Melting or Fusion Method: The fusion method is sometimes referred to as the melt method. The polymer sodium alginate and urea were melted at 60°C and then the drug was added, mixed well and cooled in an ice bath to obtain a solid mass. The solidified mass was crushed and passed through a sieve No. 22. The resulting solid dispersion was stored in a desiccator until used [24].

Solvent Melt Method: Solid dispersions of drug with sodium alginate were prepared by melt-solvent method. In this method, drug was dissolved in methanol and the solution was incorporated into the melt of sodium alginate at 165°, by pouring into it. It was then kept in an ice bath for sudden cooling. The mass was kept in the desiccator for complete drying. The solidified mass was scrapped, crushed, pulverized and passed through sieve No. 22 [25].

Characterization of Solid Dispersions

Standard Plot of Domperidone in 0.1m Hcl Buffer, (Ph 1.2): Weighed quantity of domperidone (25mg) was dissolved and the volume made up to 25ml with 0.1M Hcl buffer pH 1.2 to give a concentration of 1000 µg/ml. From this stock solution different volumes were transferred into 10 ml volumetric flasks and volume were made up to 10ml with 0.1M Hcl buffer (pH 1.2) to get different concentrations ranging from 10 to 100 µg/ml concentrations. The absorbance was measured at 287 nm against a blank using UV Spectrophotometer (Shimadzu, UV-1601 Japan).

Fourier Transforms Infrared Spectroscopy: Infrared spectroscopy was conducted using a Avatac 320-FT IR Spectrophotometer and the spectrum was recorded in the region of 4000-400 cm^{-1}. The procedure consisted of dispersing a sample (drug and solid dispersion) in KBR (200-400mg) and compressing into discs by applying a pressure of 5 tons for 5 min in a hydraulic press. The pellet was placed in the light path and the spectrum was obtained.

Percentage of Practical Yield: Percentage of practical yield was calculated to know about percent yield or efficiency of any method, thus its help in selection of appropriate method of production. Solid Dispersions were collected and weighed to determine practical yield (PY) from the following equation 1 [26].

$$\text{Practical Yield (\%)} = \frac{\text{Mass of Solid dispersions recovered (Practical mass)}}{\text{Mass of carrier and drug used in formulation (Theoretical mass)}} \times 100 \quad \text{Eq. (1)}$$

Drug Content: Solid dispersions equivalent to 10mg of domperidone were weighed accurately and dissolved in 10ml of methanol. The solution was filtered, diluted suitably and drug content was analyzed at 275 nm by UV Spectrophotometer [27]. The actual drug content was calculated using the following equation:

$$\text{Drug content (\%)} = \frac{\text{Actual amount of Solid dispersions}}{\text{Theoretical amount of Solid dispersions}} \times 100 \quad \text{Eq. (2)}$$

***In vitro* Release Study:** The dissolution studies on pure drug and solid dispersion (equivalent to 50 mg of drug) were performed. The condition of dissolution test was as follows: medium, 900 mL 0.1-M

Hcl (pH 1.2); speed, 100 rpm; temperature, 37±0.5°C; apparatus, USP type II rotating paddle. During dissolution study, 10-mL aliquot was withdrawn at different time intervals from 5 to 80 min and replaced with equal volume of fresh medium. The withdrawn samples were filtered through Whatman filter paper No. 42 and absorbance was measured at 287nm against 0.1-M Hcl blank. Cumulative percent drug dissolved was found out at each time interval and graph was plotted between cumulative percent drug dissolved and time in min.

RESULTS

Standard Plot of Domperidone in 0.1M HCL Buffer (pH 1.2): The domperidone drug content in tablet was estimated using calibration curve as shown in Fig.1.

Percentage of Practical Yield and Drug Content: The drug content of the solid dispersions was found to be between 97.4 and 99.98% and the recovery of the solid dispersions was found to be same in all the method (Table 1).

FT-Infra Red Studies (Drug-Excipient Compatibility Studies): The FT-IR spectra for domperidone, sodium alginate and all the solid dispersions of different preparation method shown that there was no interaction between them (Fig. 2-6).

***In vitro* Dissolution Study:** In this study the effect of different preparation methods for solid dispersion and pure drug were studied on the release profile of dexamethasone from sodium alginate polymer. Dissolution profiles of pure drug and different method of solid dispersions after 90min was shown in Fig. 7. The *in vitro* dissolution test showed a significant increase in the dissolution rate of solid dispersions as compared with pure domperidone.

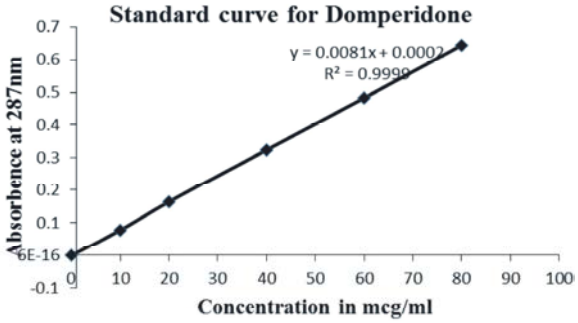

Fig.1: Standard plot for domperidone

Table 1: Effect of percentage of solid dispersion recovery and drug content

Method of preparation	1:1(drug-domperidone: polymer-sodium alginate) Solid dispersion recovery%	Drug content%
Fusion method	75	99.98
Solvent evaporation method	75	97.77
Solvent melt method	75	97.88

DISCUSSION

All the solid dispersions of different preparation method showed the presence of high drug content and low standard deviations of the results (Table 1).

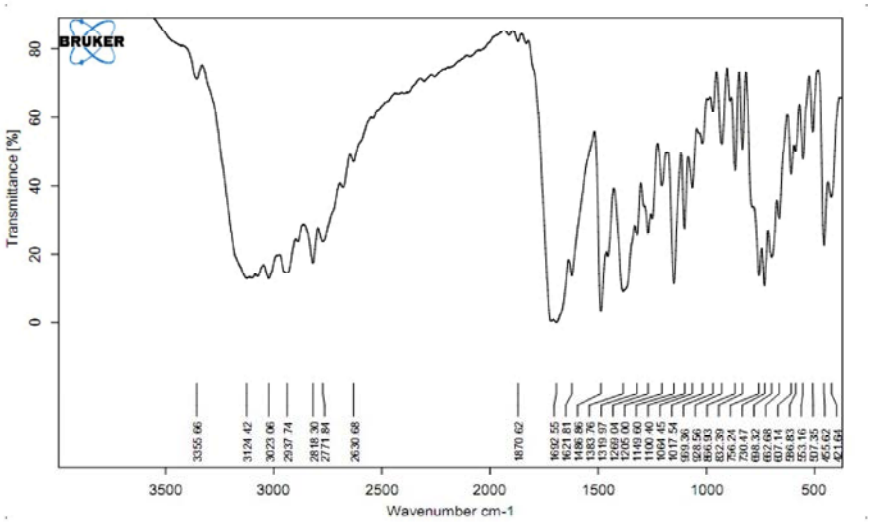

Fig. 2: FT-IR spectra of domperidone.

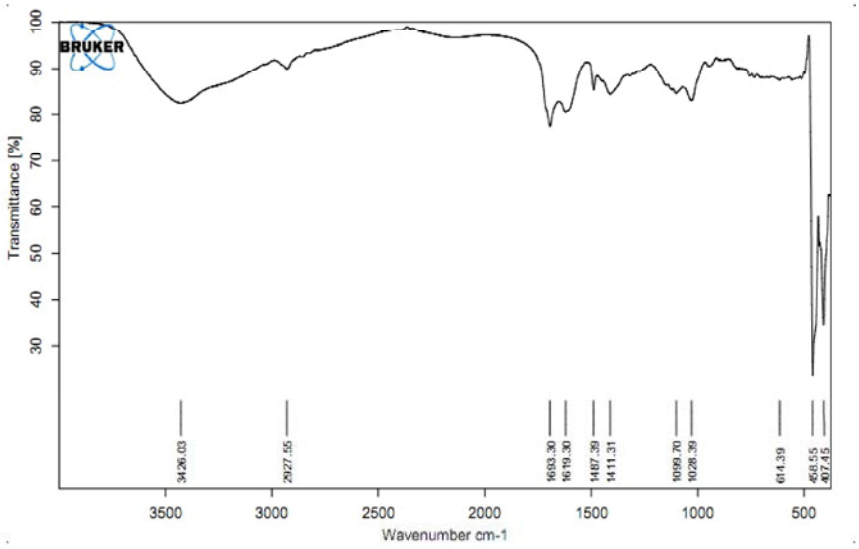

Fig .3: FT-IR spectra of sodium alginate.

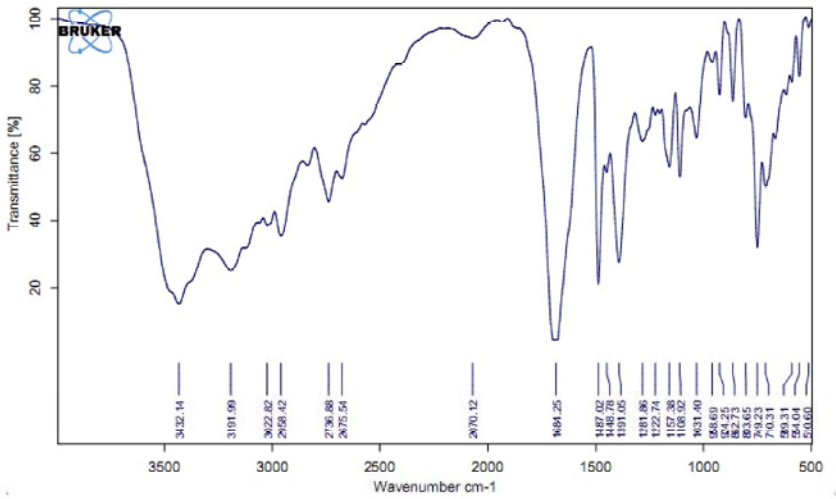

Fig. 4: FT-IR spectra of solvent melt method.

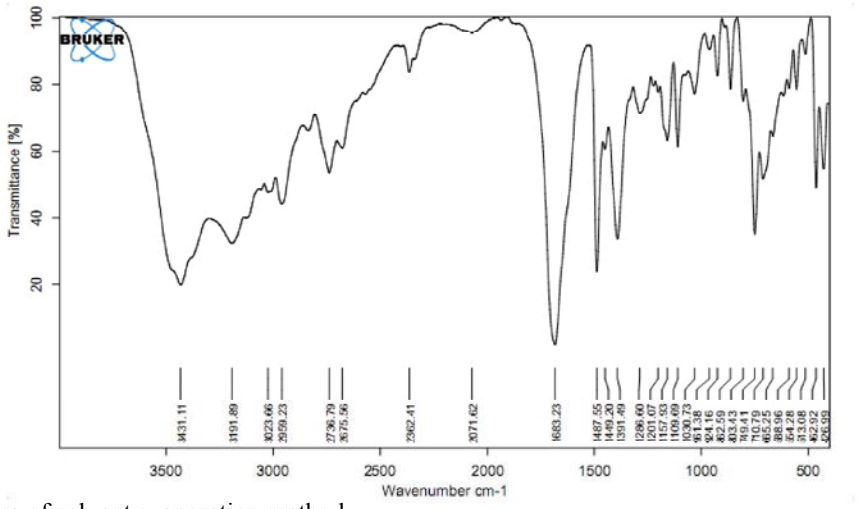

Fig. 5: FT-IR spectra of solvent evaporation method.

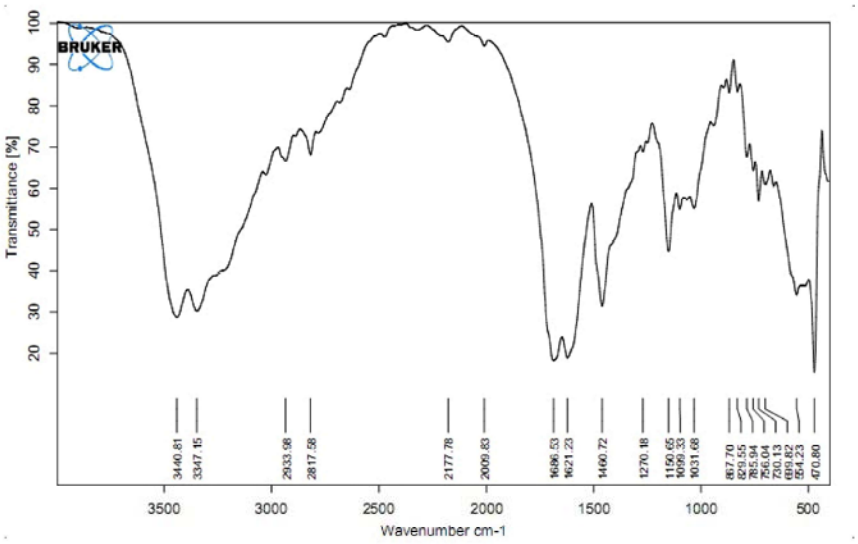

Fig. 6: FT-IR spectra of fusion method

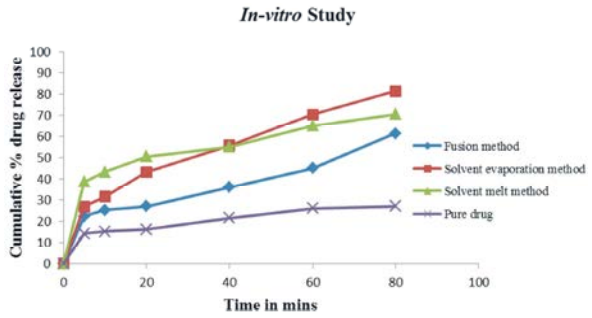

Fig. 7: Comparative dissolution profiles of domperidone solid dispersion and pure drug.

It indicates that the drug is uniformly dispersed in the powder formulation. Therefore, the method solvent evaporation, fusion and solvent melt method used in this study appears to be reproducible for preparation of solid dispersion.

In comparison with pure drug the absorption peak of the FT-IR spectra for domperidone showed no significant shift and no disappearance of characteristic peaks in all the method suggesting that there is no interaction between drug and polymers or no degradation in domperidone molecule (Fig. 3-7). The differences in transmittance may be due to varied concentration of drug.

From the *In-vitro* study, it can be clearly observed that the dissolution rate of pure drug was low because 27.14% of drug dissolved in 90 min. There was marked increase in the dissolution rate of domperidone from all the solid dispersions when compared to pure domperidone itself. The dissolution rate of drug from all the solid dispersions after 90 min was 81.39, 70.56 and 61.45%. Among the three solid dispersion method, highest improvement was observed in solid dispersions prepared by the solvent evaporation method. The increased dissolution rate may be attributed to the increased drug wettability, decreased particle size, conversion to amorphous form and solubilization of the drug due to hydrophilic carrier.

Dry mixing of drug with a hydrophilic carrier result increase in wetting and increased surface available for dissolution by reducing interfacial tension between hydrophobic drug and dissolution media. During dissolution studies, it was noted that drug carrier systems sink immediately, whereas pure drug keeps floating on the surface for a longer time interval. Thus, when such a system comes in contact with an aqueous dissolution medium, the hydrophilic carrier dissolves and results in precipitation of the embedded drug into fine particles, which increase the dissolution surface available. Moreover, other factors such as absence of aggregation and/or re-agglomeration phenomenon during dissolution and particle size reduction could be attributed to a better dissolution profile. Ford [28] and Martinez-Oharriz [29] also reviewed the mechanism of dissolution rate improvement from solid dispersion that lack of crystallinity, increased wettability and dispensability and particle size reduction considered to be important factors for dissolution rate enhancement. The release rate was increased in the following order, SEM > SMM > FM > PD.

CONCLUSIONS

In conclusion, development of domperidone prepared with sodium alginate showed better percentage yield and drug content in all the method. FT-IR study showed no interaction between the drug, polymer and the solid dispersion preparation. The *in-vitro* dissolution test showed a significant increase in the dissolution rate of solid dispersions as compared with pure domperidone. It was evident that the solid dispersion (SD) technique had improved the dissolution rate of drug to a great extent. Finally it could be concluded that solid dispersion of domperidone using hydrophilic polymers would improve the aqueous solubility, dissolution rate and thereby enhancing its systemic availability. In addition, these results indicate that dispersion technique can be an effective delivery system to improve the bioavailability of poor water soluble drugs like domperidone.

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