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PHASE SOLUBILITY STUDY OF HYDROPHOBIC DRUG DOMPERIDONE USING A NOVEL TECHNIQUE INCLUSION COMPLEX WITH β -CYCLODEXTRINE

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ABSTRACT

An inclusion complex of with a β -cyclodextrine and hydroxy propyl cellulose is a convenient new technique for enhancing the solubility of Domperidone. Phase-solubility studies demonstrated the ability of β - cyclodextrins to complex with Domperidone and increase drug solubility as well as stability also. The solid inclusion was characterized by infrared spectroscopy, differential scanning calorimetry (DSC) and element analysis. These experimental results confirmed the existence of 1:1 inclusion complex of Domperidone with β -cyclodextrin, the formation constant of complex was determined by the Enhancement of dissolution rates with increasing quantity of β -CD in the complex was observed. It was also observed that the complexes exhibit higher dissolution rates than the pure drug and physical mixture. The Apparent stability constant, 'K' for F 2 and F3 was found to be 142 M^{-1} , 200.3 M^{-1} respectively, which indicates the formation of stable complex.

Keywords: Solubility; Stability, Inclusion Method, β -cyclodextrine Complex.

INTRODUCTION

Domperidone

(DOM), or 5-chloro-1- [1-[3-(2,3-dihydro-2-oxo-1H-benzimidazol-1-yl)propyl]-4-piperidinyl]-1,3- dihydro-2H-benzimidazol-2-one [$\text{C}_{22}\text{H}_{24}\text{ClN}_5\text{O}_2$] is a dopamine antagonist used as an antiemetic for the short-term treatment of nausea and vomiting of various etiologies [1] including that associated with cancer therapy and with levodopa or bromocriptine therapy for parkinsonism [2]. Domperidone is poorly water soluble drug erratically absorbed in stomach and possess several dissolution problems thus it has a poor bioavailability [15%] [3]. The poor aqueous solubility may be one possible reason for its low bioavailability.

Cyclodextrine

Cyclodextrins are mainly used to increase the aqueous solubility and dissolution rate of drug. Among α , β , γ - β -CD are used for the study, because it has bigger

cavity size of (7.5Å) and is the least toxic among the other natural cyclodextrin. Cyclodextrins were reported to enhance topical drug delivery in the presence of water. The interior environment of a cyclodextrin cavity is hydrophilic; hence it can entrap unionized form of the molecule which too is hydrophilic, [4]. Cyclodextrins (CDs) are polysaccharides made up of six to eight d-glucose monomers connected at the one and four carbon atoms. They have a property of forming inclusion complex with various guest molecules with a suitable polarity and dimension because of their special molecular structure/hydrophobic internal cavity and hydrophilic external surface. Owing to this ability, they have found extensive application in many fields including pharmaceutical technology (to improve the aqueous solubility, dissolution rate, bioavailability and stability of drugs) [5-7]. Now, many poorly soluble drugs have been complexed by CDs to enhance solubility, chemical stability

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and bioavailability of the drugs [8,9]. When complexed with CDs, many guest molecules exhibit enhanced fluorescence efficiencies, since CD cavity can protect guest molecule excited states from nonradiative and quenching processes that normally readily occur in bulk aqueous solution [10] and the fluorimetric method is sensitive and selective, so it has been extensively used to determine the association constants of complexes [11]. The solid inclusion complex were characterized by methods include infrared spectra (IR), differential scanning calorimetry (DSC), element analysis [12-15], the cyclodextrin complex successfully observation include many atoms and have explained the experimental studies [16].

Hydroxypropyl Cellulose. Cellulose ether derivatives as hydroxypropyl Cellulose are water soluble uncharged polymers they interact with anionic surfactant in the solution resulting in rheological properties to the system. It is partially substituted poly (hydroxypropyl) ether of cellulose. It contains not less than 53.4 percent and not more than 80.5 percent of hydroxypropoxy groups. All other material used in the study of analytical grade. In the present work, we prepared the inclusion compound of Domperidone- β -cyclodextrin under microwave irradiation, and determined the complex by FTIR, X-RD studies, DSC, Phase solubility studies etc.

MATERIAL AND METHOD

MATERIAL

Domperidone (DOM), was obtained as gift samples from Trade N Trade Tumsar (Glaxo) Cyclodextrine and Hydroxypropyl Cellulose was obtained and all the chemical from the analytical grade supplied from the store room from the, SLMIOF Amgaon, India.

Preformulation Studies

Determination of Melting Point

The melting point of Domperidone was determined by capillary tube method. A small quantity of powder was placed into a capillary tube and the tube was placed in the capillary melting apparatus and the temperature was gradually increased automatically. The temperature at which powder started to melt and the temperature when all the powder gets melted were observed.

Solubility studies [17]

Drug solubility is usually determined by the equilibrium solubility method in which excess amounts of drug were taken and 10 ml of the respective distilled water and 0.1 N HCl transferred in to 100 ml stopper volumetric S- slope
So- intercept

Fourier Transform Infra Red Spectroscopy

flask and shaken for 24 hour at room temperature [25°C] samples were filtered through wattmann filter paper no.42 and aliquots were suitably diluted for estimation and measure the absorbance at 284 nm. (Shimadzu UV- 1800, Japan)

Calibration curve of Domperidone

A stock solution of Domperidone [10 mg] was prepared and transferred to 100 ml calibrated volumetric flask then 1 ml Dimethyl sulfoxide [DMSO] was added and make up the volume with 0.1N HCl. From this stock solution, 10 ml was pipette out and diluted to 100 ml with 0.1 N HCL. Further dilutions were made in order to obtain the solutions of 2, 4, 6, 8 and 10 μ g/ml respectively. Measured the absorbance in UV Spectrophotometer at μ max284 nm against reference solvent as a blank. The drug in the concentration range of 2–10 mg/ml was found to obey Beer–Lambert's law. Repeat the same procedure using distilled water as solvent. The calibration curve was plotted taking concentration on X-axis and absorbance on Y-axis

Preparation of inclusion complexes [18]

Domperidone inclusion complexes were prepared by using β - CD and HPC [1:1] with a mixture of volatile liquid (acetone) and water (1:1) and kneaded thoroughly for 30 minutes in a motor and pestle. Sufficient solvent was added to maintain paste like consistency. The paste formed obtains and dried under vacuum for 24 hours. Dried powder were scrapped, crushed, pulverized and passed through sieve no. 80 and stored in desiccators for further studies.

Phase solubility studies [19]

Phase solubility studies were performed according to the method suggest by Higuchi and Connors. An excess amount of Domperidone (10 mg) was added to 10 ml of distilled water containing rising amounts of β -CD and HPC solutions at various concentrations (0, 2, 4, 6, 8, 10 μ g/ml) in 50 ml volumetric flask . The solution were stirred at 37°C for 24 hours on a Orbital Shaking Incubator REMI Elektrotechnik Limited, (Model no. CIS-24BL). After equilibrium, the samples were filtered through Wattmann filter paper no. 42 and measure the absorbance at λ max 284 nm using a UV spectrophotometer (Shimadzu UV- 1800 Spectrophotometer, Shimadzu, Japan). The apparent 1:1 stability constant of the complex was calculated from the phase-solubility diagram using the following equation.

$$\text{Apparent stability constant } K = \frac{\text{Slope}}{S_0(1-\text{Slope})}$$

Where

The FT-IR spectra of pure drug, Drug and physical mixtures were taken by preparing KBr pellets using FTIR spectrophotometer (Varian640-IR, USA). The condition was used as follows pressure, 6-8 tons; die size,

13mm; The spectra were recorded within 4000-400cm⁻¹ wave numbers

RESULTS AND DISCUSSION

Determination of Melting Point

Domperidone is a white, crystalline odourless powder. The physical appearance was found to be similar with that of the reported standards of European Pharmacopoeia. Melting point the drugs was determined by using melting Point determination apparatus 242-244°C. This compiles the specifications of the pure drug as per European Pharmacopoeia.

Solubility studies

The solubility of Domperidone in Distil water is 3.68 µg/ml and in 0.1 N Hcl is 13.82 µg/ml. Formation of complexes between Drug, β-Cyclodextrins, and Hydroxypropyl cellulose increases the solubility compare to pure drug in both the distil water and 0.1 N HCL.

Standard curve

Discussion: As per the observations (Table.2,3) Standard curve for domperidone in 0.1 N Hcl and distal water at λ_{max} max 284 with varying concentration range of 2, 4, 6, 8, 10 µg/ It was found that the estimation of domperidone by spectrophotometric method at 284nm. The calibration curve equation for domperidone in 0.1 N HCL was obtain $Y = 0.028 X + 0.000$, with correlation coefficient $r^2 = 0.998$, and in Distil water were obtain = $0.016 X + 0.001$ with correlation coefficient $r^2 = 0.998$ respectively. This proves the linearity, of the curve.

Fourier Transform Infrared Spectroscopy FTIR

FTIR spectroscopy was used to characterize the possible interactions between drug and carrier in the solid state. The FT-IR of pure drug was characterized by C=O stretching at 1710.60 cm⁻¹, and N-H stretching at 3000 cm⁻¹. Which indicates the presence of -CONH group, asymmetric C-H stretching at 2937.38 cm⁻¹, symmetric C-H stretching at 2817.81 cm⁻¹, N-H deformation at 1693.38 cm⁻¹. sharp characteristic peaks of domperidone at 600, 700, 1192.40, 1490.12, 1490.12 & 1500 cm⁻¹. All the above characteristic peaks appear in the spectra of dispersion complex F2, and F3. Systems at same wave number which indicate no modification or interaction between the drug and polymers. Shown in figure 8.1, 8.2, and 8.3

Phase solubility studies

The phase solubility diagram for the complex formation between F2 and F3 is shown in figure 6. For F2 the regressed curve has a slope value 0.011, intercept 7.8x 10⁻²mM and correlation coefficient is $r = 0.968$ and F3 the regressed curve has a slope value 0.015, intercept 7.5x10⁻² mM and correlation coefficient is $r = 0.989$, and the phase solubility diagram figure 2 showed AL type of curve, due to the straight line had a slope less than unity; indicates the formation of complex. The apparent stability constant, K was calculated from the linear plot of the phase solubility diagram according to the equation.

$$\text{Apparent stability constant } K = \frac{\text{Slope}}{S_0(1-\text{Slope})}$$

Where, 'S₀' is the slope, and so is the intercept. The apparent stability constant, 'K' of F2 and F3 was found to be 142 M⁻¹, 200.3 M⁻¹ respectively. This indicates the formation solid complexes prepared by kneading method.

Table 1. Solubility analysis of pure drug and different ratio of polymers

S/no	Samples	Solubility Distilledwater (µg/ml)	Solubility 0.1 N Hcl (µg/ml)
1	F1	3.68	13.82
2	F2	8.416	21.85
3	F3	10.66.	30.81

F1- Pure drug, F2- Drug HPC complex [1:1], F3- Drug β-CD complex [1:1]

Discussion: The solubility of domperidone can be enhanced by Formation of complexes F2, F3. In which the formulation **F3** increase the solubility by three times as compare to pure drug

Table 2. Preparation of STD Curve of Domperidone in 0.1 N HCL

Con	Abs -1	Abs -2	Abs -3	Average	Stddev
0	0	0	0	0	0
2	0.063	0.06	0.047	0.057	0.009
4	0.143	0.114	0.099	0.119	0.022
6	0.188	0.167	0.142	0.166	0.023
8	0.244	0.227	0.221	0.231	0.012
10	0.288	0.311	0.267	0.289	0.022

Table 3. Preparation of STD curve of Domperidone in Distilled water

Con	Abs -1	Abs- 2	Abs-3	Average	Std.Dev
0	0	0	0	0	0
1	0.017	0.012	0.014	0.014	0.003
2	0.032	0.033	0.031	0.032	0.001
4	0.058	0.063	0.068	0.063	0.005
6	0.082	0.098	0.101	0.094	0.010
8	0.106	0.114	0.14	0.120	0.018
10	0.132	0.142	0.167	0.147	0.018

Figure 1. Drug + β-Cyclodextrins complex 1:1



Figure 2. Complexes 1:1.



Figure 3. sample for phase solubility studies



Figure 4. orbital shaker assembly



Figure 5. Preparation of STD Curve of Domperidone in 0.1 N HCL

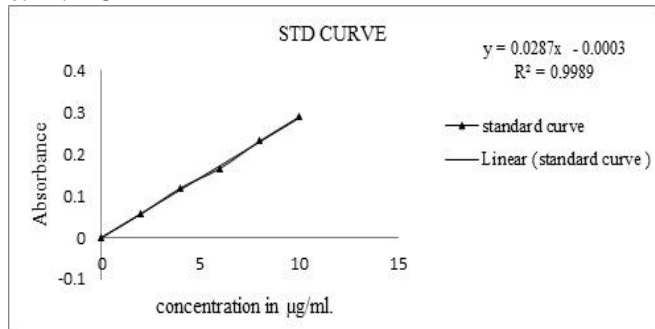


Figure 6. Preparation of STD curve of Domperidone in Distilled water

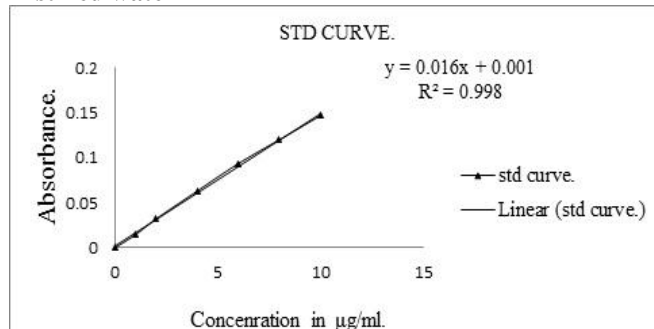


Figure 7. The phase solubility diagram Domperidone and β-Cyclodextrins and Hydroxypropyl cellulose at 28°C

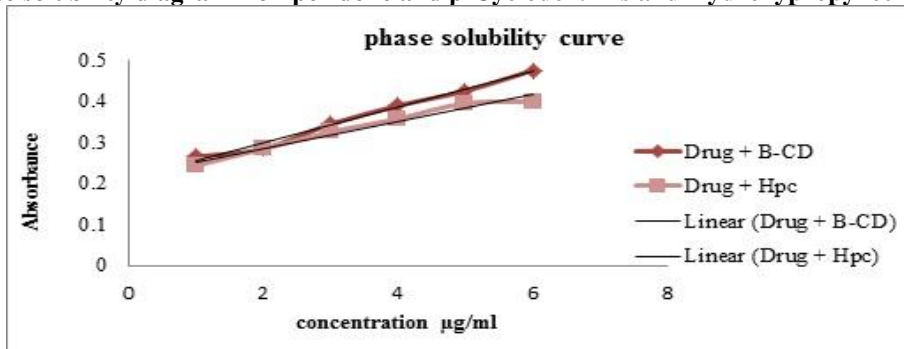
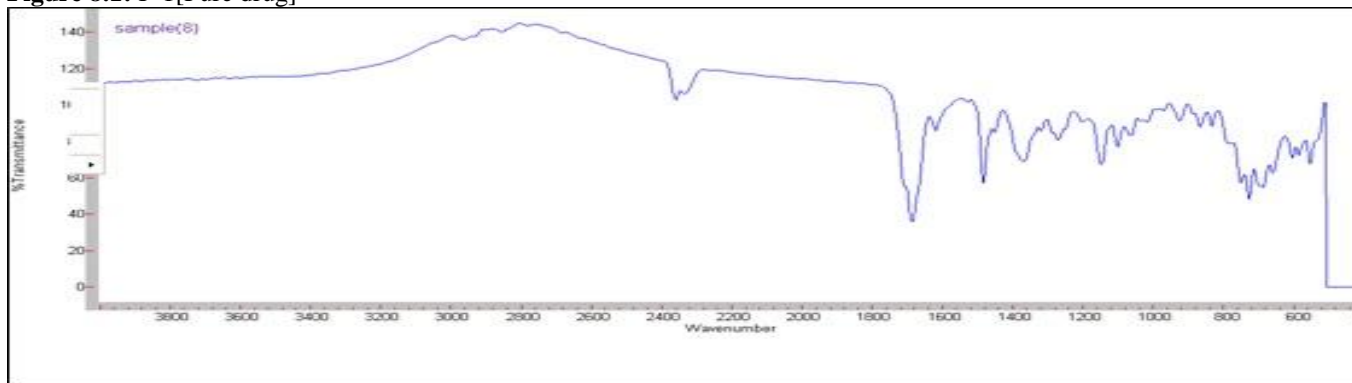
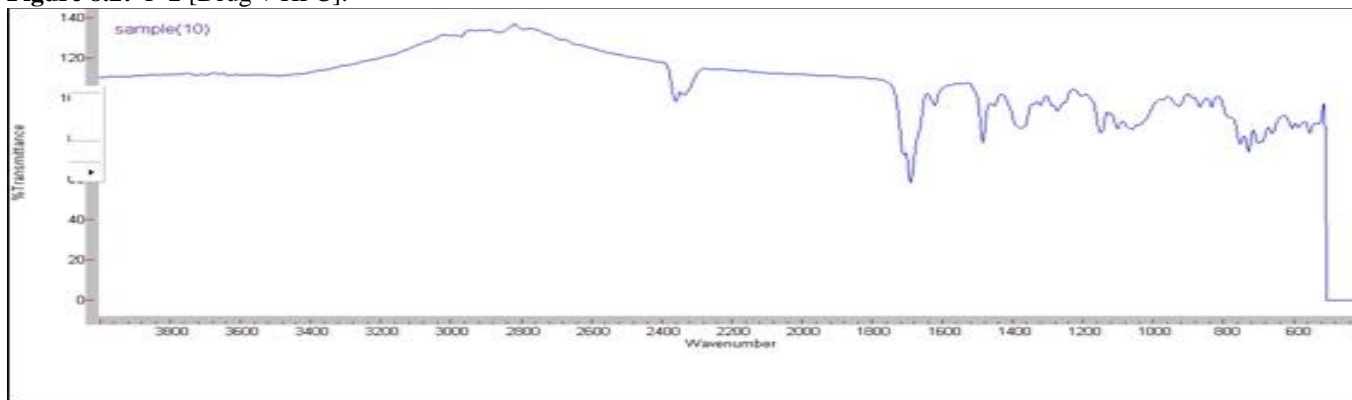
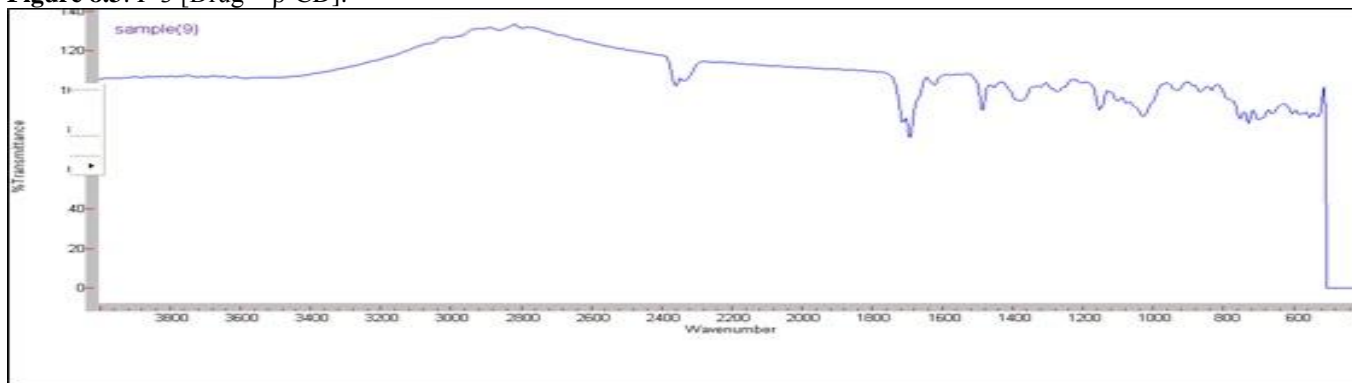


Figure 8.1: F-1 [Pure drug]**Figure 8.2:** F-2 [Drug + HPC].**Figure 8.3:** F-3 [Drug + β -CD].

CONCLUSION

The present research work is to enhance the solubility of poorly soluble drug domperidone and conversion in to granules using β -Cyclodextrins and HPC. Domperidone is a drug belongs to a *class II* of drugs called *antiemetic* used for the management of mild to moderate pain, fever, and inflammation. Domperidone having the poor solubility in water about 0.000986 mg/ml and this limits its use as solid dosage form for oral administration, erratically absorbed in stomach and possesses several dissolution-related problems thus it has poor bioavailability. Hence, by considering these facts related to

drug, attempts have been made to formulate inclusion complexes using β -Cyclodextrins and also to study the effect of preparation method. Inclusion complexes were prepared using β -Cyclodextrins in 1:1 molar ratios. The solubility of domperidone can be enhance by formation of complexes between Drug, β -Cyclodextrins, and Hydroxypropyl cellulose increase by three times as compare to pure drug as the solubility enhances dissolution rates can be increases and hence increases in bioavailability. After performing compatibilities studies FTIR all the characteristic peaks appear in the spectra of dispersion complex F2, and F3. Systems at same wave number which

indicate no modification or interaction between the drug and polymers. In Phase solubility studies it was concluded that as the concentration of polymer concentration β -CD and hydroxypropyl cellulose concentration increases, it increases the solubility of Domperidone. The phase solubility diagram Figure 7 showed AL type of curve, due to the straight line had a slope less than unity, indicates the formation of complex. The Apparent stability constant, 'K' for F 2 and F3 was found to be $142 M^{-1}$, $200.3 M^{-1}$

respectively. This indicates the formation of stable complex.

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