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ENHANCEMENT OF DOMPERIDONE DISSOLUTION RATE VIA FORMULATION OF ADSORBATES AND CO-ADSORBATES

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ABSTRACT: The aim of this study was to enhance the dissolution rate of water-insoluble, weakly basic antiemetic drug; Domperidone (DMP), through the formulation of adsorbates and co-adsorbates. Adsorption of drug onto the surface of three different adsorbents; Avicel PH 101, Florite R and Aerosil 200 was studied and Langmuir adsorption isotherms were constructed. Adsorbates of drug with the used adsorbents were prepared in different weight ratios by physical mixing, grinding and solvent evaporation methods. Co-adsorbates of drug with Aerosil 200 and Tween 80 were prepared by solvent evaporation method in different weight ratios. The prepared systems were physico-chemically characterized by Fourier- transform Infrared Spectroscopy (FT-IR), Differential Scanning Calorimetry (DSC) and powder X-ray diffractometry (P-XRD). FT-IR data confirmed the absence of any chemical interaction between DMP and the used adsorbents. P-XRD results confirmed the transformation of some systems from the crystalline state to the amorphous state which aided in the dissolution rate enhancement. Furthermore, the in-vitro dissolution rate of drug from these systems was studied which showed marked enhancement of DMP dissolution rate at both pH 1.2 and pH 6.8 (7 fold and 5 fold, respectively) compared to drug alone. It can be concluded that the dissolution rate of DMP was markedly improved via formulation of adsorbates and co-adsorbates.

INTRODUCTION: Domperidone (DMP) is 5-chloro-1-[1-[3-(2, 3 - dihydro - 2 - oxo - 1H - benzimidazol-1-yl)-propyl] 4-piperidinyl]-1, 3-dihydro-2H-benzimidazol-2-one, with a molecular formula of $C_{22}H_{24}ClN_2O_5$. It is a dopamine (D_2) receptor antagonist. DMP is used for the treatment and prevention of acute nausea and vomiting of any cause; especially cytotoxic therapy and radiotherapy.¹ DMP is practically insoluble in water (1 part in 50,000 part of water) and has a pka value of 7.9 so, it is a weakly basic drug with a very poor dissolution rate at relatively high pH values.²

This makes the absorption of drug dissolution rate-limited and lowers the oral bioavailability to 13-17%.³ The low oral bioavailability of DMP required administration of high doses which have been reported to be associated with cardiac side effects.⁴

In 2014, The European Medicines Agency (EMA) recommended reduction of dose to 30 mg daily for adults and 0.25 mg/kg up to 3 times daily for children and decided to withdraw any dosage form delivering higher doses from market.⁴ The challenge was to achieve maximum therapeutic benefits using the lowest possible dose. The aim of current study was to deal with this challenge and improve the dissolution rate of DMP via formulation of adsorbates and co-adsorbates to enhance its absorption and consequently, the oral bioavailability. Adsorption of drugs onto adsorbents helps to increase the effective surface area of drug and thus, improves the drug

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dissolution.⁵ The addition of surfactant to the adsorbates yields co-adsorbates which have the additional advantage of increasing the wettability and solubility of drug.⁶ The Adsorption of drug onto the surface of Avicel PH 101, Florite R and Aerosil 200 was studied and Langmuir adsorption isotherms were constructed. Adsorbates of drug and the used adsorbents were prepared using three different techniques; physical mixing, grinding and solvent evaporation in weight ratios of 1:1, 1:3 and 1:5 (w/w) drug to adsorbent, respectively. Co-adsorbates of drug with Tween 80 and Aerosil 200 were prepared by solvent evaporation method in weight ratios of 1:1:5, 1:3:5 and 1:5:5 (w/w/w), respectively. The prepared systems were characterized for their physico-chemical properties and in-vitro dissolution rate at two different pH values; 1.2 and 6.8.

MATERIALS AND METHODS:

Materials:

1. Domperidone (Pharco, for pharmaceutical and chemical industry, Egypt).
2. Micro crystalline cellulose (Avicel) PH 101 grade (Evans Chem. CO., Egypt).
3. Florite R (Tokuyama Soda, Tokyo, Japan).
4. Aerosil 200 (El-Nasr pharmaceuticals and chemicals CO., Egypt).
5. Tween 80® (sigma chemical CO., USA).

All other used chemicals and reagents were of pharmaceutical grade and were used as received.

Equipment:

1. Single beam spectrophotometer (JENWAY-model 6305, UK).
2. Electric sensitive balance (Precisa, Switzerland)
3. USP II dissolution apparatus (Erweka DT-D6, Heusenstamm, Germany).
4. Digital pH meter (JENWAY-model 3310, UK)

5. Vacuum oven drier (Poland).
6. Differential Scanning Calorimeter, DSC-50 (Shimadzu, Japan).
7. Fourier- transform infrared spectrometer (Shimadzu IR-470, Japan).
8. X-ray diffractometer (Philips 1710 model, Germany).
9. Vibrating uniball mill (VEB Leuchten bau-KM1, Germany).
10. Digital precise shaking water bath (DAIHAN scientific company-model WSB-45, Korea).

Methods:

Determination of Equilibrium Adsorption of Domperidone:

Phosphate buffer solution (pH 6.8) containing 20 µg/ml of drug was prepared and added to 100 mg of the investigated adsorbent in clean dry 100 ml volumetric flasks. The flasks were firmly closed and shaken at a rate of (40±2) stroke/minute in a thermostatically controlled water bath at 37± 0.5 °C. After suitable time intervals (1, 2, 4, 6, 8, 12, 18 and 24 hours), samples of 1ml were withdrawn from each test solution , filtered immediately and assayed spectrophotometrically at λmax of 284 nm for the remaining DMP content . Control test solution, containing identical concentration of DMP without adsorbent, was treated similarly to check for any drug loss. Blank solutions containing only adsorbents without drug were also treated similarly. The equilibrium time for adsorption of drug onto the surface of all the investigated adsorbents was achieved within 4-6 hours. There was no decrease in drug concentration in the control experiment confirming the absence of any drug loss due to degradation or adsorption to glass utensils during equilibration.

Construction of Langmuir Adsorption Isotherms:

Phosphate buffer solutions (pH 6.8) containing different concentrations of domperidone (10, 12, 16, 20 and 30 µg/ml) were added to 100 mg of the investigated adsorbent in clean, dry 100 ml

volumetric flasks. All samples were subjected to the same conditions and treated as previously mentioned in equilibrium adsorption study. All samples were left for 12 hours to ensure equilibrium.

Preparation of physical mixtures of drug and adsorbents:

Florite R and Avicel PH 101 were activated in vacuum drier at 120°C and 70°C for 3 and 24 hours, respectively and stored in a desiccator over calcium chloride till used. Aerosil 200 was used as received. Physical mixtures of DMP with Avicel pH 101, Florite R and Aerosil 200 at weight ratios of 1:1, 1:3 and 1:5 (w/w) drug: adsorbent were prepared by gentle blending of the desired amount of the drug and the adsorbent using a mortar and a pestle. The prepared samples were pulverized, sieved to obtain a particle size range of 125-250 µm and stored in a desiccator over calcium chloride till used.

Preparation of ground mixtures of drug and adsorbents:

Ground mixtures of the drug and the previously mentioned adsorbents at weight ratios of 1:1, 1:3 and 1:5 (w/w) drug: adsorbent were prepared by grinding the physical mixtures of drug with each adsorbent in a vibrating ball mill for 15 minutes. The prepared samples were pulverized, sieved to obtain a particle size range of 125-250 µm and stored in a desiccator over calcium chloride till used.

Preparation of loaded mixtures of drug and adsorbents:

Loaded mixtures of DMP with each adsorbent at weight ratios of 1:1, 1:3 and 1:5 (w/w) drug: adsorbent were prepared by solvent evaporation method. The desired amount of drug was dissolved in methanol. The accurately weighed adsorbent was dispersed in minimum amount of methanol and then added to the solution of drug with sufficient stirring. The solvents were removed under reduced pressure at 40°C till constant weight was obtained. The prepared samples were pulverized, sieved to obtain a particle size range of 125-250µm and stored in a desiccator over calcium chloride till used.

Preparation of domperidone co-adsorbates:

DMP co-adsorbates with Tween 80 and Aerosil 200 were prepared in weight ratios of 1:1:5, 1:3:5 and 1:5:5 ,respectively using solvent evaporation technique. The accurately measured volume of Tween 80 equivalent to the specific intended weight of surfactant (1, 3 and 5g) was added to 5 g of Aerosil 200 in a porcelain dish to prepare Tween 80: Aerosil 200 mixtures in ratios of 1:5, 3:5 and 5:5 (w/w). The obtained slurry was infrequently stirred using a glass rod for 2 hours and then dried in an oven at 110°C till constant weight was obtained. The final dried powder obtained was dispersed in minimum amount of methanol and then added to the methanolic solution containing the specified amount of drug with sufficient stirring. The solvents were removed under reduced pressure at 40°C till constant weight was obtained. The prepared samples were pulverized, sieved to obtain a particle size range of 125-250 µm and stored in a desiccator over calcium chloride till used.

Characterization of The prepared systems:

Drug content:

An accurately weighed amount of the prepared systems equivalent to 10 mg of the drug was added to 100 ml volumetric flask, dissolved in minimum amount of methanol and the volume completed to 100 ml with phosphate buffer (pH 6.8). After suitable dilution, DMP content was determined spectrophotometrically at 284 nm. Only those samples containing 100± 5% of the claimed amount of DMP were considered for further studies.

Fourier-transform infrared (FT-IR) studies:

A qualitative FT-IR analysis was performed for drug, adsorbents and the prepared systems. Samples of 1-2 mg were mixed with potassium bromide (IR grade) and compressed into discs in a compressor unit under vacuum and then scanned from 4000 to 400 cm⁻¹ with an empty pellet holder as a reference.

Differential Scanning Calorimetry (DSC) studies:

DSC thermograms were obtained by using a shimadzu DSC-50 (Japan) equipped with a software computer program. Samples of about 5mg

were placed in an aluminum pan of 50 µl capacity and 0.1mm thickness, press-sealed with aluminum cover of 0.1mm thickness. An empty pan sealed in the same way was used as a reference. Samples were heated from 30° to 300°C at a rate of 10°C min⁻¹ and nitrogen flow of 40 ml/min. Indium was used as a standard for calibrating temperature. Thermograms obtained were analyzed using TA-50 program to determine temperature and heat of fusion (ΔH) for each peak.

Powder X-ray diffractometry (P-XRD) studies:

The X-ray diffractograms were obtained using Philips 1710 diffractometer (Germany). The target was CuKα radiation operating at 40KV and a current of 40mA and a single crystal graphite monochromator was used. The diffraction patterns were achieved using continuous scan mode with 2θ ranging from 4° to 60° at a rate of 0.6°/min.

In-vitro dissolution studies:

USP dissolution apparatus II (paddle type) was used at a rotation speed of 50 rpm. Powdered samples of each preparation equivalent to 10 mg of domperidone were added to the dissolution medium (500ml buffer solution with pH 1.2 or 6.8, kept at 37±0.5°C). Pure drug was sieved to obtain a size range of 125-250 µm and treated similarly. At time intervals of 5, 15, 30, 45, 60, 90 and 120 minutes, samples (5ml) of the solution were withdrawn with a volumetric pipette, using cotton plug as a filter and replaced with an equal volume of fresh dissolution medium equilibrated at 37°C. The samples were analyzed spectrophotometrically at λ max of 284nm. Each experiment was performed in triplicate, and the mean recordings were used for calculations.

RESULTS AND DISCUSSION:

Langmuir adsorption isotherms:

The adsorption of DMP onto surface of Avicel PH101, Florite R and Aerosil 200 was evaluated using Langmuir adsorption model:⁷

$$y = x/m = k.n.C_{eq} / 1 + n.C_{eq}$$

where, (y) is the amount of DMP in millimoles (X) adsorbed per (m) grams of adsorbent, (C_{eq}) is the equilibrium concentration of drug (m.mole/L), (K) is the association constant (L/m.mole), and (n) is

the maximum amount of drug adsorbed to form monolayer under experimental conditions (limiting adsorption capacity) (m.mole/g).

Fig. (1, 2 and 3) represent typical Langmuir isotherms for adsorption of DMP onto the surface of Avicel pH101, Florite R and Aerosil 200, respectively. Langmuir isotherms were obtained by plotting (X/m) versus (C_{eq}). The curves showed typical type I Langmuir isotherms proving the formation of an adsorbed monolayer of drug onto the surface of the used adsorbents.⁸

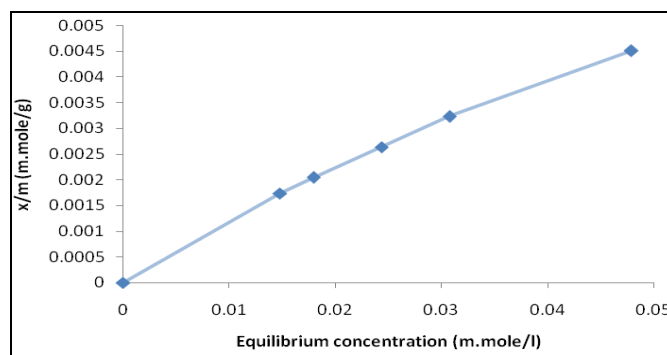


FIG.1: TYPICAL LANGMUIR ISOTHERM FOR ADSORPTION OF DMP ONTO AVICEL PH101 IN A BUFFER SOLUTION OF pH 6.8 AT 37°C.

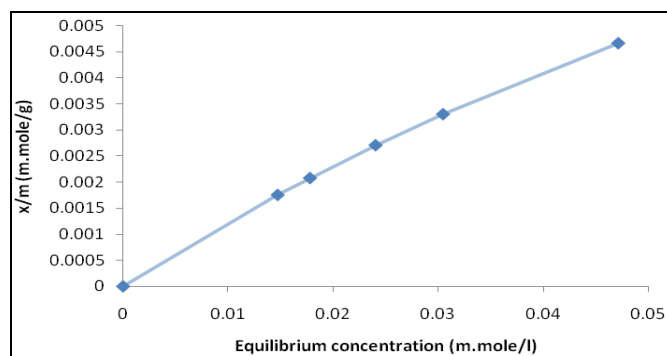


FIG.2: TYPICAL LANGMUIR ISOTHERM FOR ADSORPTION OF DMP ONTO FLORITE R IN A BUFFER SOLUTION OF pH 6.8 AT 37°C.

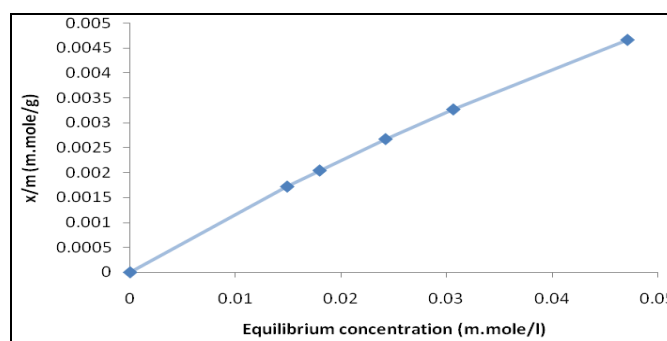


FIG.3: TYPICAL LANGMUIR ISOTHERM FOR ADSORPTION OF DMP ONTO AEROSIL 200 IN A BUFFER SOLUTION OF pH 6.8 AT 37°C.

The linear form of Langmuir equation is:

$$C_{eq}/y = C_{eq}/n + 1/n.k$$

When (C_{eq}/y) was plotted against (C_{eq}), a straight line was obtained indicating that adsorption of DMP onto the surface of the investigated adsorbents was a continuous function of the initial concentration of the drug⁹ (Fig. 4, 5 and 6).

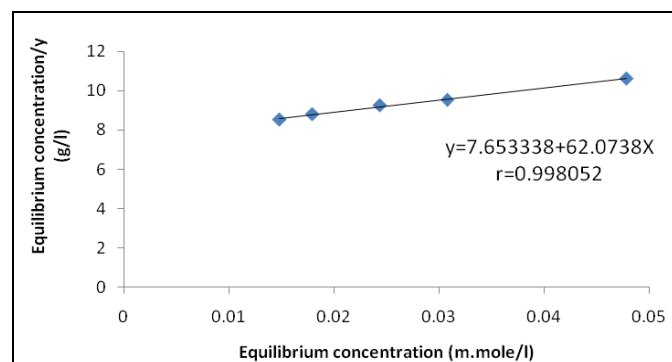


FIG.4: LINEAR LANGMUIR PLOT FOR ADSORPTION OF DMP ONTO THE SURFACE OF AVICEL PH 101 IN A BUFFER SOLUTION OF pH 6.8 AT 37°C.

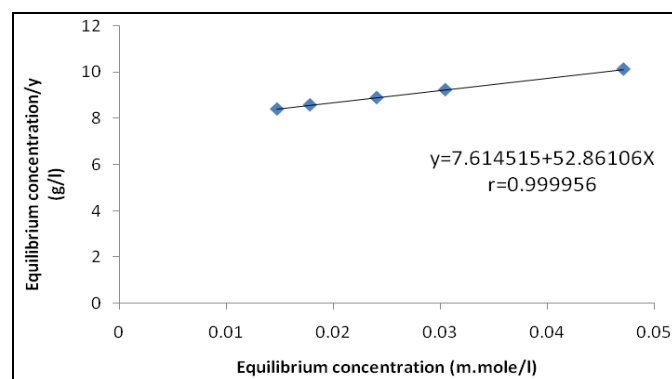


FIG.5: LINEAR LANGMUIR PLOT FOR ADSORPTION OF DMP ONTO THE SURFACE OF FLORITE R IN A BUFFER SOLUTION OF pH 6.8 AT 37°C.

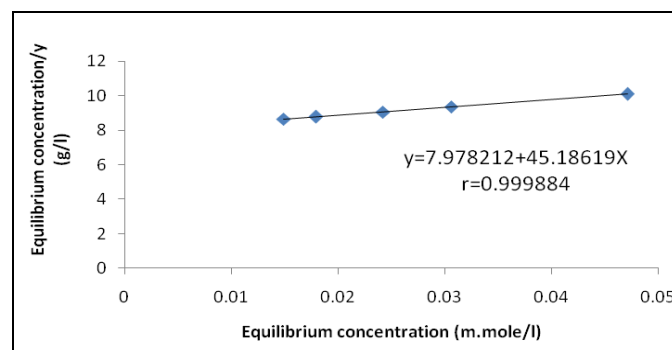


FIG.6: LINEAR LANGMUIR PLOT FOR ADSORPTION OF DMP ONTO THE SURFACE OF AEROSIL 200 IN A BUFFER SOLUTION OF pH 6.8 AT 37°C.

The maximum adsorption capacity (n) and the association constant (K) can be calculated from the

slope and intercept of the linear plots.

$$n = 1/\text{slope}$$

$$K = 1/n \cdot \text{intercept}$$

The limiting adsorption capacities of DMP onto Avicel PH 101, Florite R and Aerosil 200 were equal to 0.01611, 0.018918 and 0.022131 m.mole/g, respectively. The association constant values were equal to 8.110683, 6.942144 and 5.663699 L/m.mole, respectively. These results indicated that Aerosil 200 has the highest adsorption capacity for the drug followed by Florite R and finally, Avicel PH 101.

Drug content of the prepared systems:

UV spectroscopic assays confirmed the homogeneity of DMP content in all the investigated samples. The differences between theoretical and actual drug contents were negligible in physical mixtures, but there were slight differences between them in ground, loaded mixtures and coadsorbates (typically $98 \pm 2\%$), probably due to loss of drug during grinding or solvent evaporation.

Fourier-transform infrared (FT-IR) spectroscopic studies:

Fig. (7) shows the FT-IR spectra of DMP-Florite R systems. Domperidone (Fig.7, trace A) showed characteristic peaks at 1697 cm^{-1} (C=O stretching vibration), $3300-3500 \text{ cm}^{-1}$ (N-H stretching vibration), $3000-3100 \text{ cm}^{-1}$ (aromatic =C-H stretching vibration), $2850-3000 \text{ cm}^{-1}$ (sp^3 -C-H vibration) and several bands at $1400-1600 \text{ cm}^{-1}$ (aromatic C=C stretching vibration). Florite R (Fig.7, trace B) showed no characteristic absorption bands due to its inorganic nature (porous calcium silicate).

Physical, ground and loaded mixtures showed the same characteristic absorption bands of drug. Increasing the amount of Florite R in mixture, the absorption band of C=O group of domperidone became more broad and decreased in intensity due to dilution effect.¹⁰ Similar results were obtained with Avicel PH 101 and Aerosil 200. The results confirmed the absence of any chemical interactions between drug and the used adsorbents.

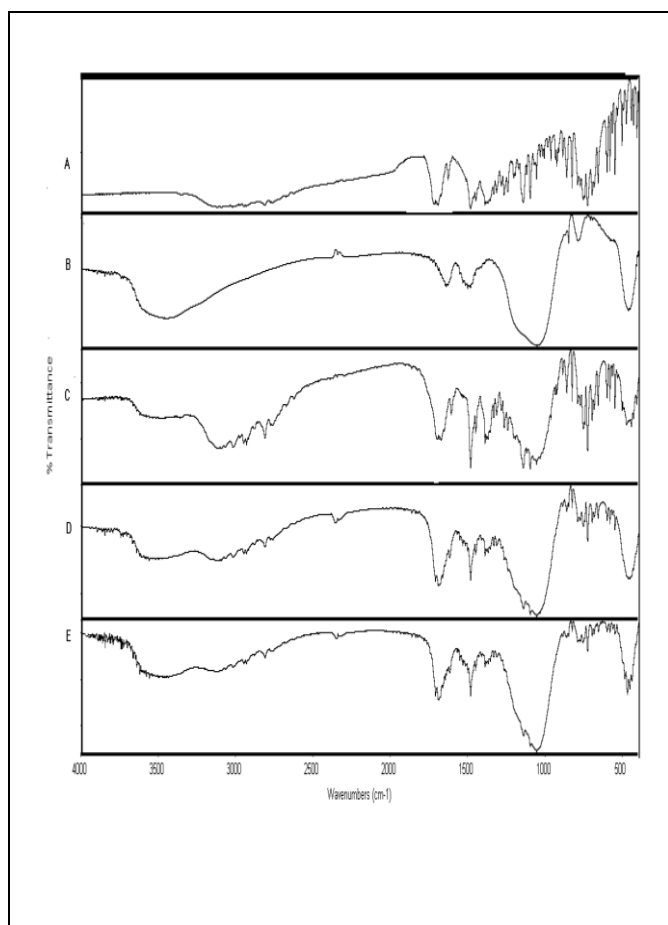


FIG.7: FT-IR SPECTRA OF DMP-FLORITE SYSTEMS. (A) DMP, (B) FLORITE R,(C) 1:5 PHYSICAL MIXTURE,(D) 1:5 GROUND MIXTURE,(E) 1:5 LOADED MIXTURE.

Differential Scanning Calorimetry (DSC) studies:

Fig. (8-11) show DSC thermograms of the prepared systems. DMP (**Fig.8-11**, trace A) showed a sharp melting endothermic peak at 252.49°C with a fusion enthalpy (ΔH) of (-94.37 J/g). This indicated that the drug was present in a pure crystalline state. Avicel pH 101 (**Fig. 8**, trace B), Florite R (**Fig.9**, trace B) and Aerosil 200 (**Fig.10** and **11**, trace B) showed no endothermic peaks up to 300°C. Increasing the amount of adsorbent in physical mixtures (**Fig.8-10**, trace C), the melting endothermic peak of drug was decreased in intensity and fusion enthalpy due to dilution effect.⁵ **Fig. (11)** shows the DSC thermograms of DMP-Tween80-Aerosil 200 co-adsorbates. It was obvious that the melting endothermic peak of DMP was severely decreased in intensity and fusion enthalpy in case of ground and loaded mixtures due to reduction of crystallinity resulted from grinding and solvent evaporation methods. The melting endothermic

peak of drug was completely disappeared in **fig.(9**, traces E and F), **Fig. (10**, traces D, E, F and G) and **Fig. (11**, traces C, D and E) suggesting that drug was changed to the amorphous state¹¹ which was confirmed by P-XRD studies as shown later.

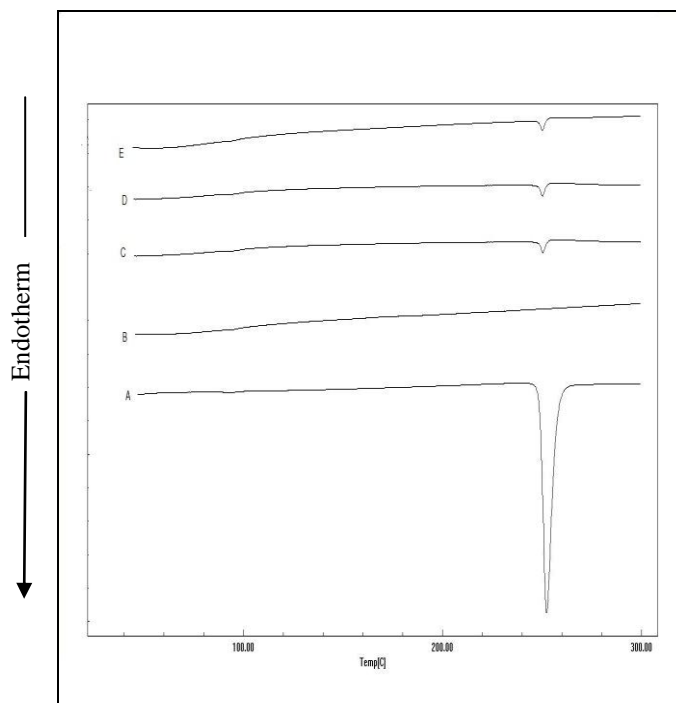


FIG. 8: DSC THERMOGRAMS OF DMP-AVICEL SYSTEMS.(A) DMP (B) AVICEL PH 101 (C) 1:5 PHYSICAL MIXTURE (D) 1:5 GROUND MIXTURE (E) 1:5 LOADED MIXTURE.

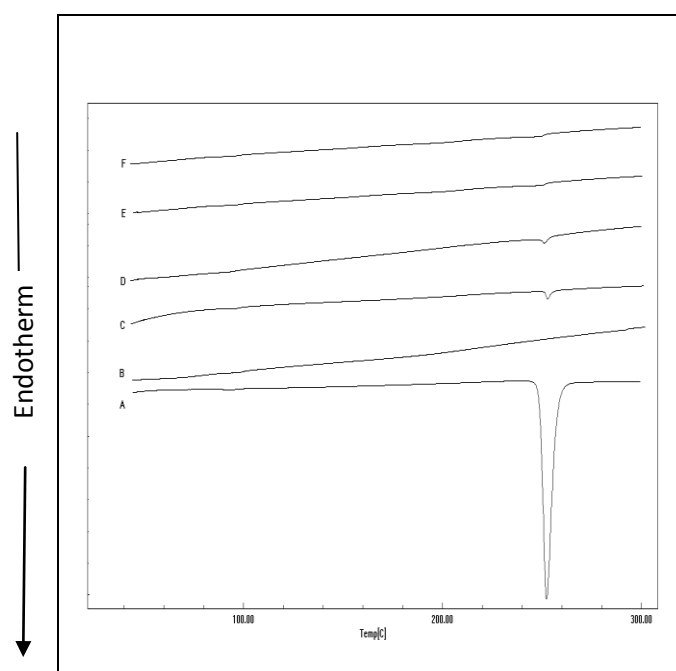


FIG.9: DSC THERMOGRAMS OF DMP-FLORITE R SYSTEMS.(A) DMP (B) FLORITE R (C) 1:5 PHYSICAL MIXTURE (D) 1:5 GROUND MIXTURE (E) 1:3 LOADED MIXTURE (F) 1:5 LOADED MIXTURE.

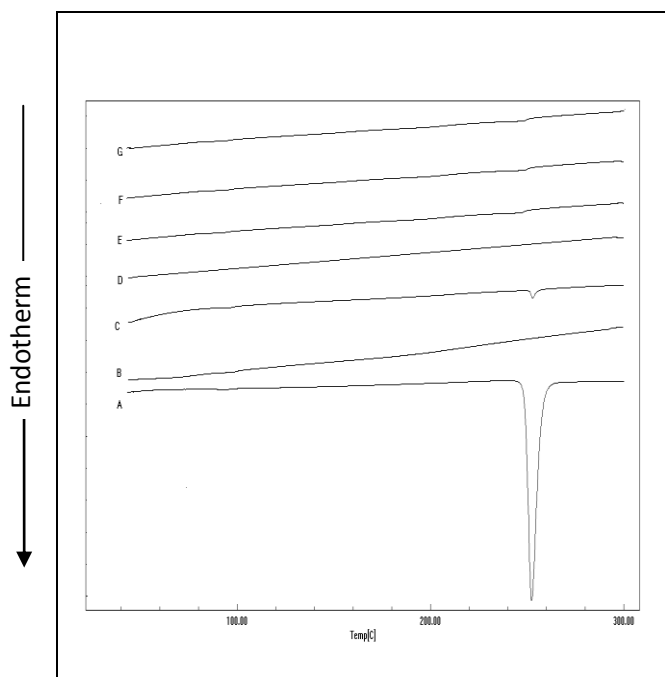


FIG.10: DSC THERMOGRAMS OF DMP-AEROSIL SYSTEMS. (A) DMP (B) AEROSIL 200 (C) 1:5 PHYSICAL MIXTURE (D) 1:3 GROUND MIXTURE (E) 1:5 GROUND MIXTURE (F) 1:3 LOADED MIXTURE (G) 1:5 LOADED MIXTURE.

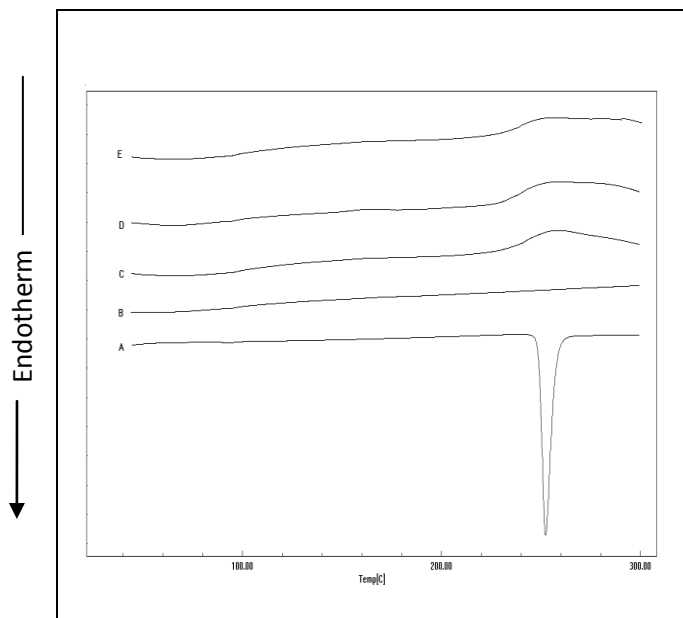


FIG.11: DSC THERMOGRAMS OF DMP CO-ADSORBATES. (A) DMP (B) AEROSIL 200 (C) 1:1:5 CO-ADSORBATE (D) 1:3:5 CO-ADSORBATE (E) 1:5:5 CO-ADSORBATE.

Powder X-ray diffraction (P-X-RD) studies:

Fig.(12-14) show powder x-ray diffractograms of DMP-Florite R, DMP-Aerosil 200 and DMP co-adsorbates systems, respectively. Pure drug (**Fig.12-14**, trace A) showed strong peaks of crystallinity which were completely disappeared in **Fig.(12**, traces C and D), **Fig.(13**, traces C,D,E and

F) and **Fig.(14**,traces C, D and E) confirming the transformation of DMP from the crystalline state to the amorphous state in these systems ¹² as suggested from DSC results mentioned before.

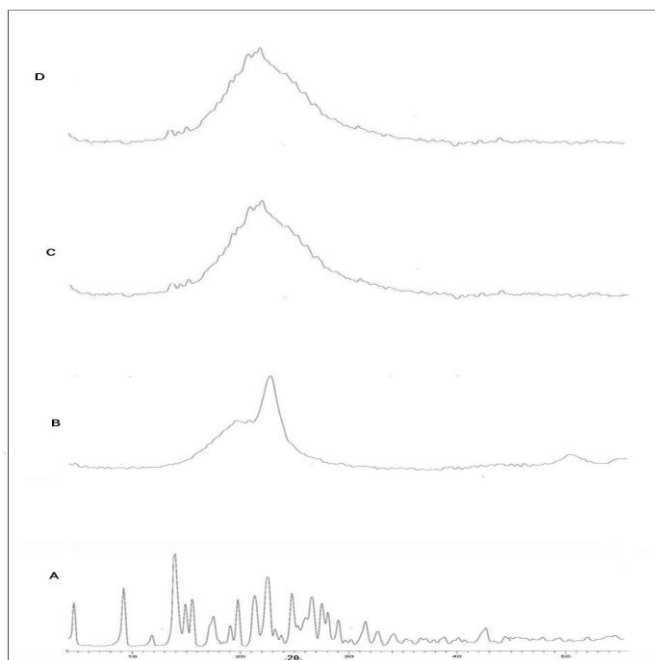


FIG.12: POWDER X-RAY DIFFRACTOGRAMS OF DMP-FLORITE SYSTEMS. (A) DMP, (B) FLORITE R, (C) 1:3 LOADED MIXTURE, (D) 1:5 LOADED MIXTURE.

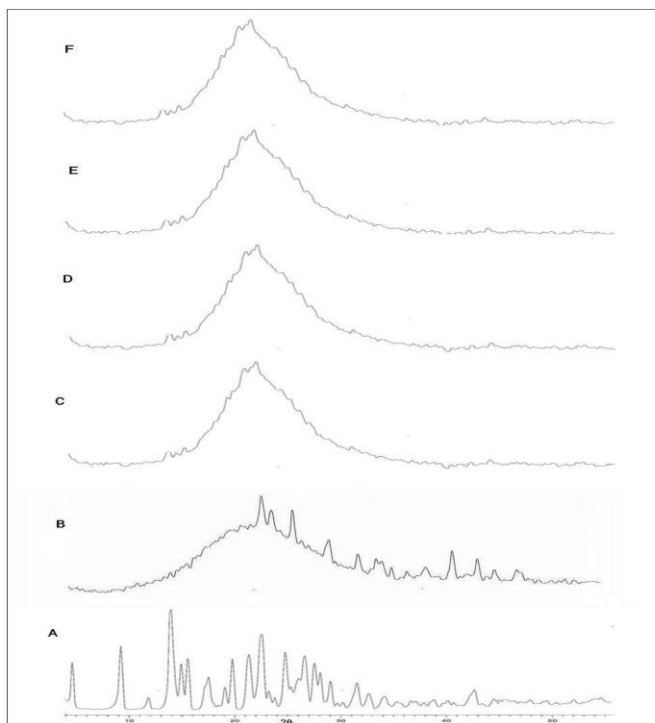


FIG.13: POWDER X-RAY DIFFRACTOGRAMS OF DMP-AEROSIL SYSTEMS. (A) DMP, (B) AEROSIL 200 ,(C) 1:3 GROUND MIXTURE, (D) 1:5 GROUND MIXTURE, (E) 1:3 LOADED MIXTURE, (F) 1:5 LOADED MIXTURE.

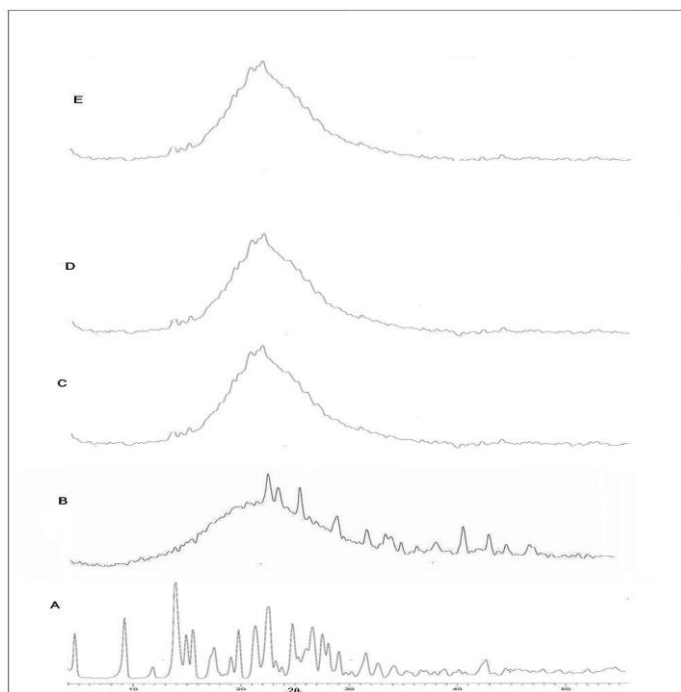


FIG.14: POWDER X-RAY DIFFRACTOGRAMS OF DMP-TWEEEN 80-AEROSIL 200 COADSORBATES. (A)DMP, (B) AEROSIL 200, (C) 1:1:5, (D) 1:3:5, (E) 1:5:5.

***In-vitro* dissolution studies:**

The dissolution profiles of domperidone from the various prepared systems are shown in **Fig. (15-20)**. All prepared systems showed higher dissolution rates than the untreated drug. The drug was released from the different prepared systems in the order of: Aerosil 200 systems > Florite R systems > Avicel pH101 systems. This was the same order of adsorbing power as indicated from Langmuir adsorption isotherms mentioned before. These results confirmed that adsorption effectively participated in the enhancement of drug dissolution rate. Within each system, the order of drug release was: loaded mixtures > ground mixtures > physical mixtures.

This can be explained by drug deposition on more extensive surface areas in case of loaded and ground mixtures than physical mixtures.¹³ Moreover, in some ground and loaded mixtures, the drug was changed to the amorphous state which has higher solubility and dissolution rate than crystalline state.¹⁴ Increasing drug: adsorbent ratio in mixture from 1:1 to 1:5, the dissolution rate was increased. It is obvious that all co-adsorbates showed the highest dissolution rate among all prepared systems. This can be attributed to the combination of adsorption effect in addition to

wetting effect of surfactant in co-adsorbates which was responsible for enhancement of solubility and dissolution of drug compared with adsorbates with adsorption effect only.⁶ Increasing amount of surfactant in the system, the release of drug was enhanced. The order of drug release from all systems at different pH values was: pH1.2 > pH 6.8. This can be explained by the weakly basic nature of drug (pka=7.9) favoring lower pH values that induce drug ionization and consequently, improve the solubility and dissolution rate of drug.¹⁵

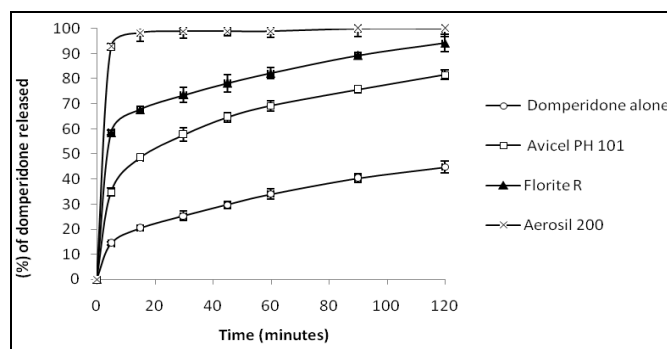


FIG.15: EFFECT OF ADSORBENT TYPE ON RELEASE PROFILES OF DMP FROM 1:5 (DRUG: ADSORBENT) LOADED MIXTURES IN A BUFFER SOLUTION OF pH 1.2.

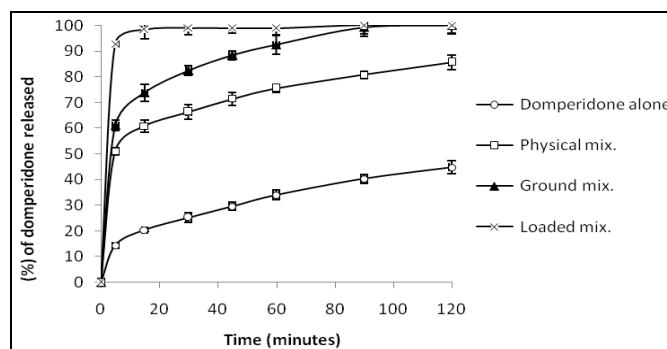


FIG.16: COMPARISON OF DMP RELEASE FROM PHYSICAL, GROUND AND LOADED MIXTURES CONTAINING DRUG AND AEROSIL 200 IN WEIGHT RATIO OF 1:5 IN A BUFFER SOLUTION OF pH 1.2.

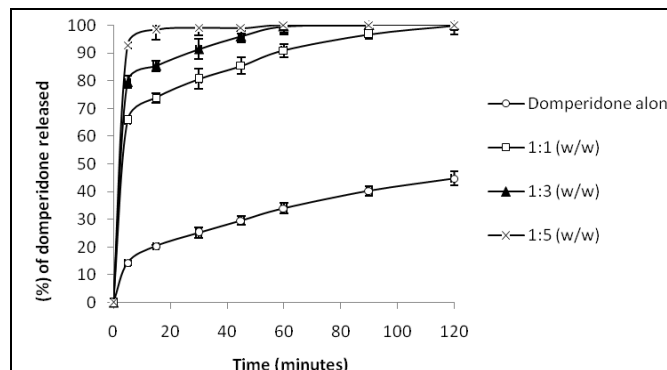


FIG.17: EFFECT OF DIFFERENT WEIGHT RATIOS OF AEROSIL 200 ON THE RELEASE OF DMP FROM ITS LOADED MIXTURES IN A BUFFER SOLUTION OF pH 1.2.

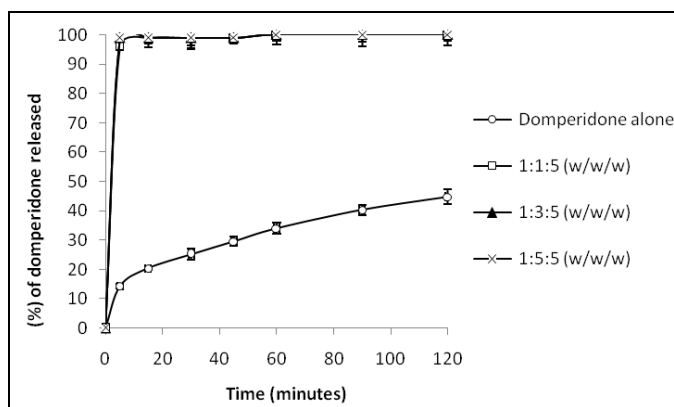


FIG.18: RELEASE PROFILES OF DMP FROM THE PREPARED CO-ADSORBATES IN A BUFFER SOLUTION OF pH 1.2.

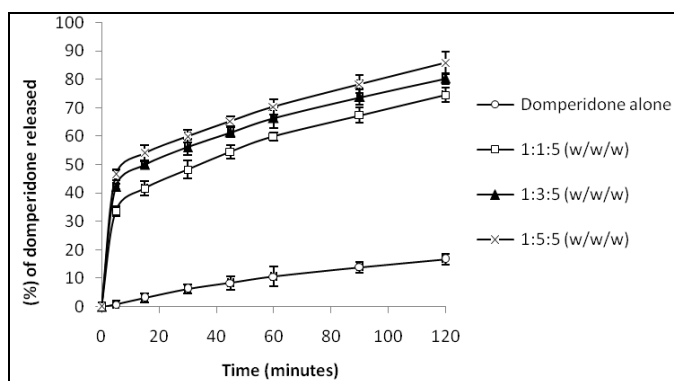


FIG.19: RELEASE PROFILES OF DMP FROM THE PREPARED CO-ADSORBATES IN A BUFFER SOLUTION OF pH 6.8.

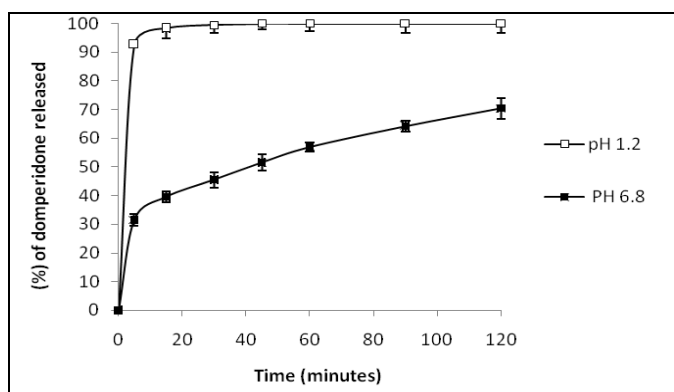


FIG.20: EFFECT OF pH ON THE RELEASE OF DMP FROM ITS LOADED MIXTURES WITH AEROSIL 200 IN WEIGHT RATIO OF 1:5.

CONCLUSION: FT-IR studies confirmed the absence of any chemical interactions between DMP and the used adsorbents. Adsorption studies confirmed the adsorption of domperidone onto the surface of the used adsorbents and showed type I Langmuir adsorption isotherms. DSC and P-XRD data confirmed the transformation of drug from the crystalline state to the amorphous state in some ground and loaded mixtures, especially at high

drug: adsorbent ratios. All co-adsorbates showed crystalline-to-amorphous transitions. The enhancement of domperidone dissolution rate can be attributed to many factors including: the increase in drug surface area, reduction of crystallinity, crystalline-to-amorphous transitions and surfactant-induced increase in drug wettability. Domperidone release from the prepared systems was pH-dependent and more favored at low pH values.

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