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Preparation and Characterization of Novel Co-Crystal Forms of Domperidone

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A B S T R A C T

Domperidone is a widely used antiemetic, poorly water soluble drug, erratically absorbed in stomach and possess several dissolution-related problems. The co-crystal formation by supramolecular approach has proven to be advantageous over the various methods of improving solubility due to its simple mode of preparation, where the stability as well as the solubility of the drug is improved. The co-crystals of Domperidone were prepared using Succinic acid as a co-former (1:1, 1:2 & 1:3) by cooling crystallization technique and characterized by IR, DSC, SEM and XRD studies. The *in vitro* dissolution studies were also performed. In distilled water, the solubility of domperidone in the Co crystal 1, 2, and 3 has shown increase in solubility compared to pure drug by 43.84, 47.54, and 52.3 folds respectively. In pH 1.2 HCl buffer solution, the solubility of domperidone in Cocrystals 1, 2 and 3 has shown increase in solubility compared to pure drug by 1.18, 1.10 and 1.05 folds respectively. Drug content of domperidone cocrystals 1, 2 and 3 was found to be 95.13%, 93.47% and 85.44% respectively. Percentage practical yield of domperidone cocrystals 1, 2 and 3 was found to be 74.21%, 60.51% and 56.48% respectively. The in-vitro dissolution studies, when compared to the formulation of Domperidone the prepared cocrystal-3(1:3) has shown maximum drug release of 89.45% with water and cocrystal-1(1:1) has shown maximum drug release of 87.76% with 0.01 N HCL as a dissolution medium.

Keywords: Co-Crystal, Domperidone, Succinic acid, supramolecular approach

A R T I C L E I N F O

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1. Introduction

Poor water soluble drugs pose significant hurdles for drug bioavailability that in turn affect in vivo efficacy and safety in all stages of formulation [R. Vir Prasad]. Improving the solubility of drugs is currently one of the main challenges for the pharmaceutical industry. A pharmaceutical co-crystal can be designed with the intention to improve the solid-state properties of an API without affecting its intrinsic structure [Fleischman S.G, Kuduva S.S, McMahon J.A, Moulton B, Walsh R.B, Rodriguez-Hornedo N and Zaworotko M.J]. It is also referred as molecular complexes. Co-crystals are multiple component structures whose components interact by non-covalent interactions such as hydrogen bonding or other weak intermolecular interactions rather than by ion pairing [McMahon J.A, Bis J.A, Vishweshwar P, Shattock T.R, McLaughlin O.L and Zaworotko M.J.] [Sharma C.V.K and Zaworotko M.J]. Domperidone is an anti-emetic and gastroprokinetic. It is a D2 antagonist and is used for the treatment and prevention of acute nausea and vomiting in adults from any cause specifically; cytotoxic therapy and radiotherapy, nausea and vomiting associated with l-dopa and bromocriptine treatment for parkinsonian patients. Domperidone being the class II drug according to the BCS classification having low solubility and high permeability, the rate limiting steps in attaining desired bioavailability. Hence the co-crystals of Domperidone were prepared using Succinic acid as a co-former by cooling crystallization technique.

2. Materials and Methods

Materials

Domperidone (Matrix Pvt. Ltd., Hyderabad), Succinic acid (SD fine chem., Mumbai), Hydrochloric acid (SD fine chem., Mumbai).

Preparation of Crystals

The accurately weighed molar concentration of drug (0.425mg) and co-former, (1:1 molar ratio) were dissolved in sufficient amount of solvent on slow heating until complete dissolution of drug and left for slow evaporation for 24hrs and observed for formation of cocrystals [Gagniere. E]. The crystals were isolated by filtration through a membrane (0.45 µm) and dried in the air. Trails were made with different coformers like succinic acid, salicylic acid, tartaric acid, citric acid, urea and nicotinamide by using solvents like water, methanol etc.,. From the trails it was found that Co-crystals of Domperidone were formed using succinic acid (1:1, 1:2 and 1:3) as coformer. Hence further studies were continued by synthesizing Co-crystals of Domperidone with succinic acid in the ratios 1:1, 1:2 and 1:3.

Characterization of prepared co-crystals

FT-IR, microscopic, DSC, SEM and XRD studies have been performed for the prepared co crystals.

FT-IR studies: IR spectroscopy was conducted using a FTIR Spectrophotometer (Thermo-IR 200) and Potassium bromide pellet method was employed and background spectrum was collected under identical conditions. The spectrum of Domperidone, Succinic acid and prepared co-crystals were recorded in the wavelength region of 4000–400 cm−1 [Callear S.K].

DSC studies

Thermal analysis of Domperidone, Succinic acid and prepared cocrystals were recorded on a DSC (NETZSCH DSC 204). The temperature axis and cell constant of DSC were previously calibrated with indium. A heating rate of 100C/min was employed with nitrogen pursing. Powder samples (15-30 mg) was weighed into an aluminum pan and analyzed as sealed with pin holes and an empty aluminum pan was used as reference [Wenger M and Bernstein J].

Scanning electron microscopy (SEM):

The surface characteristics of Domperidone, Succinic acid and prepared cocrystals were studied by SEM (ZEISS Electron Microscope, EVO MA15). The specimens were scanned with an electron beam of acceleration potential of 20 kV and the images were collected as secondary electron mode [Basavoju S, Bostrom D and Velaga S.P].

Powder X-Ray Diffraction (P-XRD):

The pXRD were undertaken to investigate the crystalline nature of Domperidone, Succinic acid and prepared cocrystals. The study was carried out using X-Ray Diffractometer using Cu kα radiation. The tube operated at 45 kV, 9mA and data was collected over an angular range from 0 to 500 2θ of the diffraction angle in continuous scan mode using a step size of 0.050 2θ and a time of 0.1s [Soanes C and Stevenson A.].

Evaluation of Cocrystals

Dissolution studies

The dissolution of cocrystals were studied using USP Type II dissolution apparatus containing 900ml capacity maintained at 37±0.5 0C and stirred at 75 rpm. Dissolution studies have been performed for the formulation of Domperidone and prepared co-crystals in pH-1.2 HCl buffer and water. 5 mL of sample was withdrawn after suitable time interval and replaced each time with 5mL fresh medium. The solutions were immediately filtered through 0.45 mm membrane filter, diluted and the concentration of drug was determined with the help of UV spectrophotometer (Schimadzu) at wavelength of 284nm. Percentage of drug dissolved was calculated by plotting time on X- axis against % cumulative drug release on Y-axis [Sonia dhiman *et al*.,].

Saturation Solubility studies

Solubility measurements were performed according to the method of Higuchi and Connors (1965). Drug solubility studies were performed by adding excess amounts of Domperidone and prepared co-crystals to water and pH-1.2 HCl buffer in separate vials. The vials containing drug and cocrystals were shaken at 37.0±0.5 º C for 48 h in water bath shaker (Remi Pvt Ltd, Mumbai). After 48 hr, samples were filtered through a 0.45-µm filter paper and analyzed in UV spectrophotometer at wavelength of 284nm. Solubility studies were performed in triplicate (n=3) [Sammour et al.].

Percentage practical yields

Percentage practical yield of prepared Cocrystals was calculated to know about percent yield or efficiency of method. Cocrystals were collected and weighed to determine practical yield (PY) from the following equation.

Percentage of practical yield = $\frac{\text{practical yield}}{\text{theoritical yield}}$ x 100

Drug Content

From each batch of prepared Cocrystals three samples of 10 mg were taken and analyzed for drug content. 10 mg of each sample was weighed and transferred in 100 ml standard flasks and volume was made up to 100 ml with pH-1.2 HCl buffer. The solutions were filtered through a 0.45µ membrane filter and diluted. One ml from above the solution was transferred into a 10 ml standard flasks and volume made up to 10 ml with HCl buffer. Absorbance of the solutions was measured at 284 nm.

3. Results and Discussion

Microscopic studies:

Optical microscopic studies of pure domperidone, succinc acid and crystal form 1, 2, and 3 are shown in the fig. no 1.

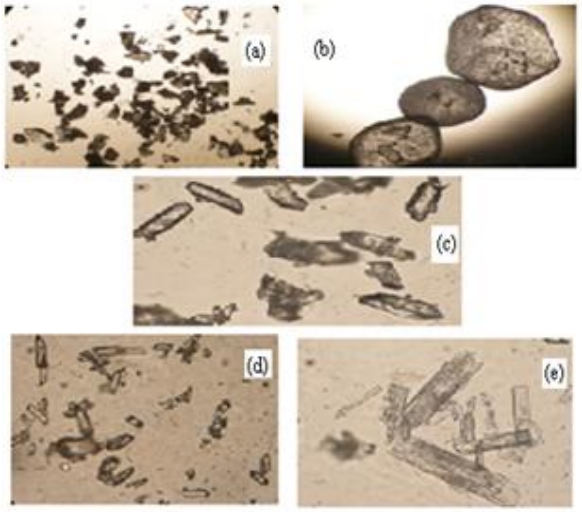

Figure 1: Optical microscopic images of (a) Domperidone, (b) succinic acid, (c) Co-crystal - 1, (d) Co-crystal - 2 and (e) Co-crystal-3

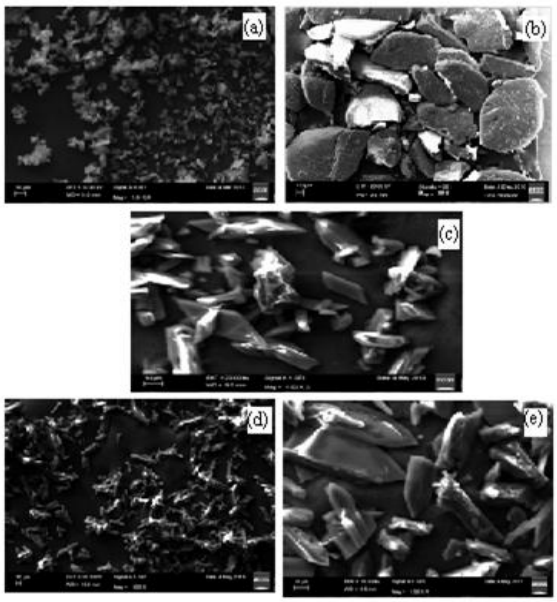

Figure 2: SEM images of (a) Domperidone, (b) succinic acid, (c) Co-crystal-1, (d) Co-crystal-2 and (e) Co-crystal- 3

Scanning electron microscopy (SEM)

SEM photographs of Domperidone, succinic acid and crystal form 1, 2 and 3 shown in figure no 2. SEM images reveal that the prepared co-crystals differ in their appearance from that of pure domperidone and succinic acid. This indicates formation of co-crystals.

FTIR studies

The FT-IR spectrum of Domperidone showed a strong C=O stretch band around 1687.06 cm−1 and CO-NH stretching at 3069.72 cm−1. FTIR spectrum of succinic acid showed a strong peak at 1208 cm−1 is a characteristic peak of dicarboxylic acid. The prepared co-crystal shows absence of CO-NH at 3069.72 cm−1 and shifting of characteristic peak 1687.06 cm−1 of amide to 1678.54, 1678.96 and 1695.27 cm−1 in crystal form 1, 2 and 3 respectively. It indicates the formation of crystal forms 1, 2 and 3 by carboxylic acid-amide heterosynthon. The IR spectra and interpretation for Domperidone, succinic acid and crystal form 1, 2 and 3 were presented in figure no 3.

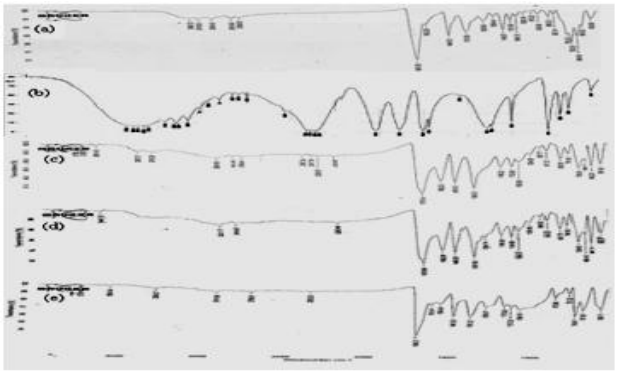

Figure 3: IR spectrum of (a) Cocrystal I, (b) Cocrystal II and (c) Cocrystal III

Differential scanning calorimetry (DSC)

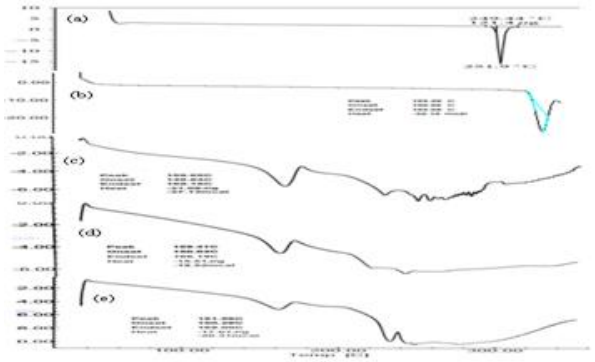

Figure 4: DSC thermo grams of (a) Domperidone, (b) succinic acid, (c) Co-crystal-1, (d) Co-crystal-2 and (e) Co-crystal-3

DSC experiments were carried out to study the thermal behavior of the crystal form 1, 2 and 3 in relation to the individual components (figure no 4). DSC study of Domperidone and succinic acid shows endothermic peak at 251.9^{0}C and 195.20^{0}C while DSC study of prepared cocrystals 1, 2 and 3 shows sharp endothermic value at 159.69^{0}C, 159.31^{0}C and 161.56^{0}C. The sharp endothermic

values of crystal forms 1,2 and 3 and the individual components agreed with the measured melting range in the melting point determination. The thermal profile of crystal form 1, 2 and 3 was distinct, with a different melting transition from that seen with either of the individual components. This indicates the formation of novel crystal forms 1, 2 and 3 of Domperidone with succinic acid.

X-Ray powder Diffraction Studies

XRPD Studies of Co-crystal-1

The X-ray powder diffraction (XRD) spectra of prepared co-crystal-1 shows peak at 14.1130^0 which has 100% relative intensity. The decrease in intensity of drug peak at 15.7250^0 and 26.8350^0 were observed. The increase in intensity of drug peak at 14.400^0 and 22.7840^0 were observed. New peaks were appeared at 18.7306^0 and 24.4644^0. This indicates formation of new crystalline lattice.

XRPD Studies of Co-crystal-3

The X-ray powder diffraction (XRD) spectra of prepared co-crystal-3 shows peak at 25.67^0 which has 100% relative intensity. The decrease in intensity of drug peak at 17.68^0 and 22.78^0 were observed. The increase in intensity of drug peak at 15.72^0 and 25.04^0 were observed. New peaks were appeared at 23.2828^0 and 24.3500^0. This indicates formation of new crystalline lattice. Figure no 5 indicates the XRPD pattern of pure drug, crystal form 1 and crystal form 3.

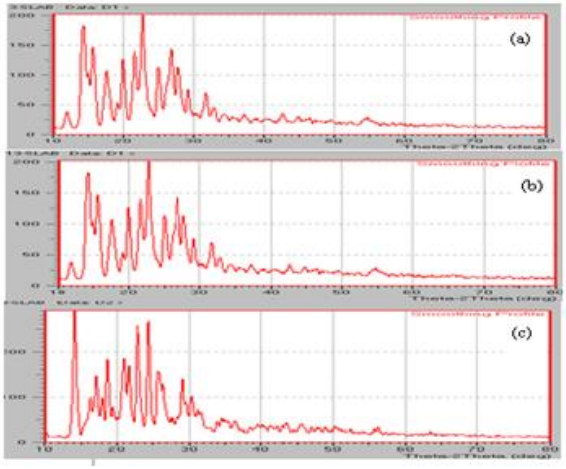

Figure 5: XRPD Pattern of (a) Domperidone and (b) Co-crystal –1 (c) Co-crystal –3

Dissolution Studies: Dissolution data in pH 1.2 HCl buffer

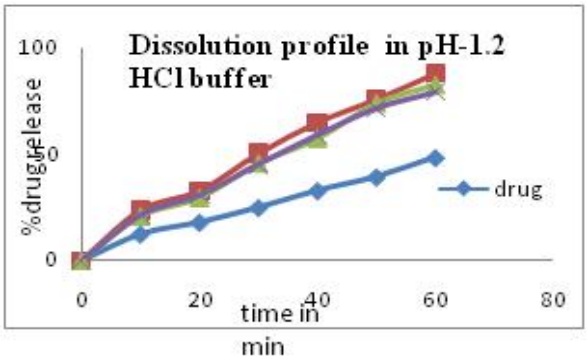

Figure 6: Dissolution profile of pure drug and prepared crystal forms in pH-1.2 HCl

Release kinetics

The data obtained from invitro studies is subjected to zero order, first order, Higuchi model, krosmeyer model, hixsoncrowell model. The % drug release of Crystal form I, II and III shown maximum drug release of 87.76%, 82.56% and 78.88% respectively in pH1.2 HCl buffer and 81.67%, 85.67% and 89.45% respectively in distilled water. From the above dissolution data it is clear that the co-crystal forms of drug showed enhanced release when compared to the pure drug. In pH 1.2 HCl buffer, zero order kinetic model has shown maximum R^2 values for drug, Co-crystal-1, 2 and 3 of about 0.992,0.988, 0.991 and 0.987 respectively. In water, krosmeyer model for drug, zero order kinetic model and first order kinetic model for Co-crystal-1&3, zero order kinetic model for Co-crystal-2 has shown maximum R^2 values of about 0.999, 0.997, 0.993 and 0.989 respectively.

Saturation Solubility studies

The solubility of domperidone in raw domperidone and domperidone Cocrystals is presented in Table 6. In distilled water, the solubility of domperidone in the Cocrystal 1, 2, and 3 was 456, 494 and 544 μg/mL, 43.84, 47.54, and 52.3 - fold higher than that of raw domperidone (10μg/mL) respectively. In pH 1.2 HCl buffer solution, the solubility of domperidone in Co crystals 1, 2 and 3 were 501, 465 and 454 μg/mL, **1.18, 1.10 and 1.05** - fold higher than that of raw domperidone (429 μg/mL), respectively.

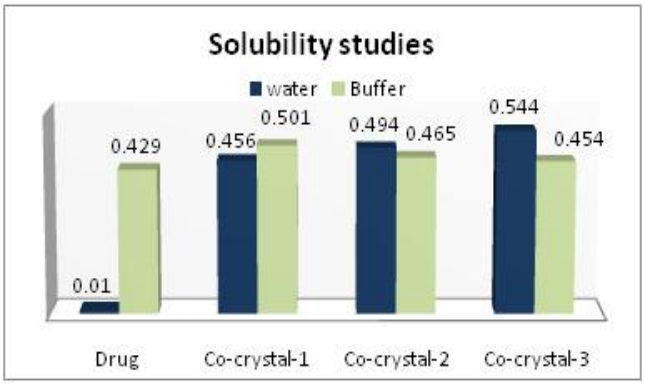

Figure 8: Solubility of drug and cocrystals in water and buffer

4. Conclusion

The main aim of the study is to prepare and evaluate the co-crystals of Domperidone using Succinic acid as a co-former, in order to attain the improved solubility of Domperidone. The co-crystals of Domperidone were prepared using Succinic acid as a co-former (1:1, 1:2 & 1:3) by cooling crystallization technique. The FTIR, DSC and SEM studies proved the formation of novel cocrystals. From the in-vitro dissolution studies, when compared to the formulation of Domperidone the prepared cocrystal-3(1:3) has shown maximum drug release of 89.45% with water and cocrystal-1(1:1) has shown max drug release of 87.76% with 0.01 N HCL as a dissolution medium. Novel co-crystals of Domperidone and Succinic acid prepared by crystallization technique have shown increase in Solubility when compared to the pure drug.

Table 1: Dissolution data in pH-1.2 HCl buffer

S.No	Time (min)	% Drug release (mean ± S.D, n=3)			
		Pure drug	**Co-crystal-1**	**Co-crystal-2**	**Co-crystal-3**
1	0	0	0	0	0
2	10	12.36 ± 0.18	23.67±0.67	20.89±0.54	21.39±0.39
3	20	17.91±0.42	32.48±0.93	29.44±0.57	30.68±0.68
4	30	24.84±0.73	50.23±0.51	45.67±0.32	45.13±0.37
5	40	32.78±0.26	64.87±0.27	57.32±0.09	58.94±0.74
6	50	39.24±0.45	75.65±0.84	73.88±0.24	71.42±0.83
7	60	48.34±0.34	87.76±0.36	82.56±0.53	78.88±0.39

Table 2: Release parameters of drug and prepared co-crystal in pH-1.2 HCl

Release kinetics		Zero order kinetics	First order kinetics	Higuchi model	Krosmeyer model	Hixsoncrowell model
Drug	**R^2**	**0.992**	**0.992**	0.939	0.983	0.966
	m	-0.763	-0.763	6.035	0.763	-0.005
	C	2.176	97.82	-4.466	0.296	4.600
Co-crystal-1	**R^2**	**0.988**	0.174	0.952	0.877	0.966
	m	1.427	-0.654	11.38	2.283	-0.005
	c	4.991	70.07	-7.905	-1.991	4.600
Co-crystal-2	**R^2**	**0.991**	0.135	0.938	0.890	0.966
	m	1.362	-0.575	10.77	2.257	-0.005
	c	3.372	70.51	-8.453	-1.986	4.600
Co-crystal-3	**R^2**	**0.987**	0.129	0.953	0.884	0.966
	m	1.303	-0.556	10.41	2.247	-0.005
	c	4.674	69.90	-7.168	-1.968	4.600

Table 3: Dissolution data in water

S.No	Time (min)	% Drug release (mean ± S.D, n=3)			
		Pure drug	**Co-crystal-1**	**Co-crystal-2**	**Co-crystal-3**
1	0	0	0	0	0
2	10	5.17±0.36	17.21±0.16	18.47±0.30	24.19±0.29
3	20	8.39±0.52	29.83±0.08	27.85±0.71	35.58±0.44
4	30	11.48±0.78	42.19±0.45	47.47±0.56	49.67±0.11
5	40	14.25±0.84	57.45±0.62	61.54±0.39	64.75±0.83
6	50	17.02±0.96	71.54±0.26	76.13±0.14	79.21±0.67
7	60	19.56±0.21	81.67±0.58	85.76±0.62	89.45±0.54

Table no: 4 Release parameters of drug and prepared co-crystal in water

Release kinetics		Zero order kinetics	First order kinetics	Higuchi model	Krosmeyer model	Hixsoncrowell model
Drug	**R^2**	0.986	0.986	0.966	**0.999**	0.966
	m	0.315	-0.315	2.535	0.745	-0.005
	c	1.384	98.61	-1.568	-0.038	4.600
Co-crystal-1	**R^2**	**0.997**	**0.997**	0.930	**0.997**	0.966
	m	1.361	-1.361	10.69	0.884	-0.005
	c	1.988	98.01	-9.485	0.337	4.600
Co-crystal-2	**R^2**	**0.993**	0.969	0.925	0.885	0.966
	m	1.451	-1.214	11.38	0.823	-0.005
	c	1.786	100.2	-10.38	0.350	4.600
Co-crystal-3	**R^2**	**0.989**	**0.989**	0.954	0.955	0.966
	m	1.455	-1.271	11.61	0.841	-0.005
	c	5.311	99.34	-7.874	0.358	4.600

Table 5: % yield of domperidone cocrystals

S.No	Formulation	Percentage yield
1	Co-crystal-1	74.21%
2	Co-crystal-2	60.51%
3	Co-crystal-3	56.48%

Table 6: Solubility studies of domperidone cocrystals

S.No	Formulation	Solubility(mg/ml)	
		water	pH-1.2 Hcl buffer
1	Drug	0.010	0.429
2	Co-crystal-1	0.456	0.501
3	Co-crystal-2	0.494	0.465
4	Co-crystal-3	0.544	0.454

Table 7: Drug content of domperidone cocrystals

S.No	Formulation	Drug content
1	Co-crystal-1	95.13±0.28%
2	Co-crystal-2	93.47±0.35%
3	Co-crystal-3	85.44±0.14%

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