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STUDY ON THE SOLUBILITY, DISSOLUTION, STABILITY AND MICROMETRIC PROPERTIES OF DEXLANSOPRAZOLE VIA CO CRYSTALLIZATION TECHNIQUES

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ABSTRACT:

Dexlansoprazole, a proton-pump inhibitor used in peptic ulcers, gastro-oesophageal-reflux disorder,Zollinger-Ellison syndrome and in H.pylori infections. TheDexlansoprazole is unstable at acidic pH, undergoes degradation in stomach. To prevent the degradation in stomach, dosage forms are supplied as enteric-coated tablets or granules encapsulated in gelatin capsules. The efficiency of such dosage forms depends upon the extent of coating, solubility of coating material, type of dosage forms; in addition this it is insoluble in water, having poor bioavailability. To overcome these major drawbacks ofDexlansoprazole, an novel technique: cocrystallizationwas attempted, to produce a stable, enhancement in solubility and improved micromeriticproperties ofDexlansoprazole. Co-crystals consists of API and a stoichiometric amount of a pharmaceutically acceptable co-crystal former. Pharmaceutical Co-crystals are non-ionic supramolecular complexes and can be used to address physical property issues such as solubility, stability and bioavailability in pharmaceutical development without changing the chemical composition of the API. Co-crystal is a crystalline entity formed by two different or more molecular entities where the intermolecular interactions are weak forces like hydrogen bonding and π- π stacking. FTIR revealed that there is no formation of hydrogen bonding between drug and co-former; hence it states that co-crystals are not formed, but XRD and DSC states that there is a formation of some physical interaction, partial crystalline and amorphous form which is a new crystal lattice.

KEYWORDS: co-crystallization, dissolution behaviour, micromeritic properties.

INTRODUCTION:

Omeprazole, a proton-pump inhibitor is widelyprescribed for the treatment of peptic ulcer, Zollinger- Ellison syndrome, Gastro-oesophageal reflux disease (GERD), H.pylori infection and NSAID associated ulcers. Its oral bioavailability (40-50%) in humans is poor, due to acid sensitivity and first pass metabolism.

Attempts were made earlier to improve the bioavailability by formulating it as enteric-coated granules encapsulated in gelatin shell and enteric-coatedtablets etc. The efficiency of such dosage forms depends upon the number of parameters such as extent of coating, solubility of coating material and type of dosage form[1]

The maximum development and interest area is being diverted to co-crystallization. Co-crystals are homogeneous solid phases containing two or more neutral molecular components in a crystal lattice with defined stoichiometric proportions, which are solids at room temperature and are held together by weak interactions, mainly hydrogen bonding. Pharmaceutical co-crystals can enhance the essential properties of the APIs such as flowability, chemical stability, compressibility and hygroscopicity. Co-crystallization can be achieved only when the physiochemical properties like Hygroscopicity, solubility, micromeriticproperties and compactionbehaviour of the formulation is to be improved at one step. Co-crystals basically consists of two components that are the API and the coformer, the co-former can be any other excipient or API which when given in combination reduces the dose and also the side effects. Changing the co-former will also changes the pharmaceutical properties, chemical stability, bioavailability, solubility, melting point,moisture uptake, dissolution.

As mentioned earlier co-crystallization is the most dynamically developing group of solid pharmaceutical substances, it is a very vast area. Hence, they can be divided into co-crystal anhydrates, co-crystal hydrates (solvates), anhydrates of co-crystals of salts and hydrates (solvates) of co-crystals of salts [2, 3].

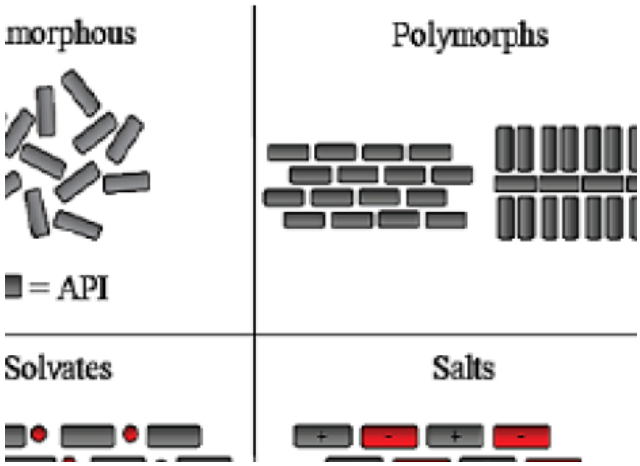


Figure.1 Comparison of co-crystals with other solid forms

Table .1 Methods used for co-crystal preparation [10]

Solidbasedmethods	**Solutionbasedmethods**	**Supercriticalfluidmethods**	**Electrically assistedmethods**
Co-grinding/drygrinding	Isothermalslurryconversion	Supercriticalslurrycrystallization	Sono-crystallization
Solventdropgrinding	Slowevaporation	Supercritical anti-solvent (SAS) andgasanti-solvent(GAS)	Microwaveassistance
Extrusion	Assistedevaporativeco-crystallization	Supercriticalassistedspraydrying	
Hotmeltextrusion	Spraydrying		
Highshearwetgranulation	Reactiveco-crystallization		
	Coolingco-crystallization		
	Antisolventaddition		

MATERIALS AND METHODS:

Materials:

Omeprazole (USP) was obtained as a gift sample from Rawchem Laboratories Pvt. Ltd. (Hyderabad, India).PVP, magnesium chloride, sodium bicarbonate, Methanol, Ethanol, Acetone, 2-propanol, Sodium dihydrogen orthophosphate dihydrate, Disodium hydrogen orthophosphate dihydrate (AR grade) were obtained from different commercial suppliers.

Methods:

Experimental attempts to PrepareDexlansoprazoleCocrystals:

To prepareDexlansoprazole co-crystal, a best co-former should be selected first with hydrogen bonding donor and acceptor ability. All the dicarboxylic acids, esters, ethers, some drugs and excipients can have good conformer character. ButDexlansoprazole is a basic drug, it is unstable in acidic medium, hence co-former must be a basic compound with donor, acceptor ability. Cogrinding method, solvent drop grinding method, slurry crystallization method, slow evaporation method were failed due to instability, hygroscopicity, photosensitivity and thermolebilityofDexlansoprazole. Then basic compounds were selected and preparation method was optimized and finalized to anti solvent addition method.

Table. 2 Experiments attempted to make co-crystals ofDexlansoprazole

Compound	**Co-formersattempted**	**Method ofpreparation**	**Inference**
OMEPRAZOLE	Dicarboxylic acids	Co-grinding	Unstable preparation
	PVP	**Antisolvent addition***	**Stable crystallinesubstance obtained.**
	PVP	Co-grinding	Unstable preparation
	PVP	Solventdrop grinding	Unstable preparation
	Calcium carbonate	Slow evaporation	Unstable preparation

Magnesium carbonate	Co-grinding	Nocrystal formed
PEG	Co-grinding	Nocrystal formed
Sodium carbonate	Slurry crystallization	Unstable preparation
PVA	Co-grinding	Unstable preparation

Method of crystals preparation:

Anti–solvent addition method:

Pharmaceutical crystals ofDexlansoprazole were prepared with PVP as co-former, magnesium chloride and sodium bicarbonate as basic substances for maintaining stability in basic pH with different solvents like acetone, methanol, ethanol, 2-propanol by anti solvent addition method. crystal was prepared by dissolving 1:1 molar ratio ofDexlansoprazole and PVP in 10ml of solvents separately followed by addition of both solutions to magnetic stirrer, allow to mix thoroughly for 20 min, 20 ml of 2% magnesium chloride solution (cool water at 10^{O}C -20^{O}C) severs as anti-solvent is added slowly to the preparation, a turbidity is formed initially gradually it produces precipitate allow to stir continuously for about 2 hrs. Then filtered and dried at 40˚C and stored in vialsat cool and dark place.

Characterization studies of prepared crystals:

Melting point:

Melting point of pureDexlansoprazole, co-formers and cocrystalswere obtained by capillary method using liquid paraffin. The capillary filled with drug powder was placed in melting point apparatus and then liquid paraffin was heated, then drug is melt the melting point of drug powder was noted.

Differential Scanning Calorimetry (DSC):

Thermal analysis ofDexlansoprazole, co-former and prepared crystal were recorded individually on DSC (Q200), Waters. The samples were scanned at 10^{O}C/min over atemperature range of 50^{O}- 400^{O}C with nitrogen purgingin aluminium pan.

Fourier Transform Infrared (FT-IR) Studies:

FT-IR of pureDexlansoprazole and prepared crystals spectra were recorded individually by a Spectrum RXI, Perkin Elmer FTIR spectrophotometer by mixing them with potassium bromide. Scans were recorded in the range of 400-4000 cm-1 at spectral resolution of 4 cm-1.

Powder X-Ray Diffraction:

The X-ray diffractogram were generated using a Brukerdiffractometer D8 Advance. Multiscans over 10-60 minutes were employed over the 2θ- range 10-80^{O}, witha scan speed 4^{O}/min.

RESULTS AND DISCUSSION:

Table3.physicalcharacterizationsstudiesofpreparationswithdifferentbasiccompoundsandsolvents.

S. NO	CODE	CO-CRYSTALCOMPONENTS	2% BASICCOMPOUND	SOLVENT	MELTING POINT(^{O}C)	SOLUBILITY mg/ml
1.	CO1	Omeprazole+PVP	$NaHCO_3$	Ethanol	142	0.794
2.	CO2*	Omeprazole+PVP	$MgCl_2$	Ethanol	135	1.0*
3.	CO3	Omeprazole+PVP	$NaHCO_3$	Acetone	137	0.822
4.	CO4	Omeprazole+PVP	$MgCl_2$	Acetone	135	0.799
5.	CO5	Omeprazole+PVP	$NaHCO_3$	Methanol	145	0.810
6.	CO6	Omeprazole+PVP	$MgCl_2$	Methanol	134	0.832
7.	CO7	Omeprazole+PVP	$NaHCO_3$	2-Propranol	144	0.816
8.	CO8	Omeprazole+PVP	$MgCl_2$	2-Propranol	136	0.438
9.	-------	Omeprazole	----------	----------	146	0.31

*Markisdenotedforthesignificantinthesolubilityandselectedforpreparationofcrystals.

From the table 2, solubility and melting point data ofdifferent preparations were reported. CO 2 code preparation is having enhanced in solubility when compared with pureDexlansoprazole. Thus it is chosen for further characterizations studies and dissolution studies.

Melting Point:

Discussion

Melting point is amongst the physicochemical propertiesof co-crystals. It is the temperature of solid and liquid phase equilibrium. This test was used as a preliminary test for confirmation of co-crystal formation. When the co-crystals are formed the melting point changes and comes in between the melting point of two individual molecules. If such results are obtained it can be confirmed that the co-crystals are formed.[9] It was found that the melting point of the crystals 135 ^{O}Cshowed a significant deviation with respect to the melting point of pure drugDexlansoprazole 146^{O}C and the individual co-former PVP 174^{O}C indicating there must be some interactions between pure and co-former. [3]

Characterization by DSC

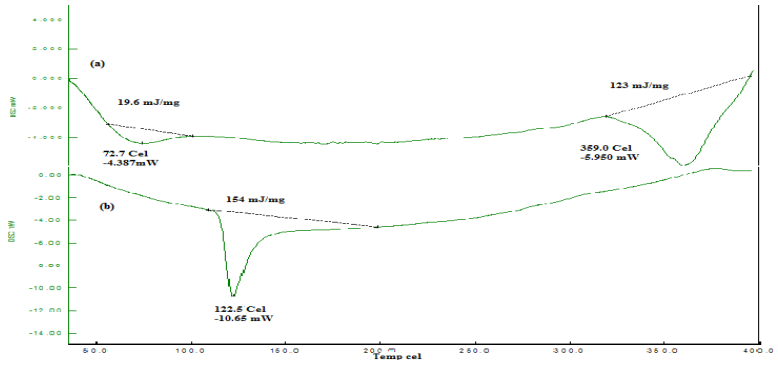


Figure 2. DSC ofDexlansoprazole-PVP crystals (a) pureDexlansoprazole (b)

DISCUSSION:

From the fig 2 DSC thermograms, it was observed thatthe prepared crystals were different in pattern and intensity, as compared to pureDexlansoprazole, which indicates their interaction. This shift in the melting point is due to the change in crystal lattice of theDexlansoprazolein presence of co-former, forming a relatively different crystal lattice. The DSC thermogram of pureDexlansoprazole(b) shows sharp melting peak at 122.5°C while DSC scan of their prepared crystals (a)shows a large broad peak at 72.7°C followed by another quite broad peak at 359°C depicting that melting peak of bothDexlansoprazole have shifted to lower and PVP have shifted to higher temperatures. These changes occurred as a consequence of interaction induced by thermal energy between the drug and the co-former, during the DSC scan of sample. The DSC thermogramforDexlansoprazole-PVP crystal shows a broad peak at 72.7°C followed by a sharp melting peak at 359°C this DSC scan of crystals suggesting the formation of a new phase.

Fourier Transform Infrared (FT-IR) Studies:

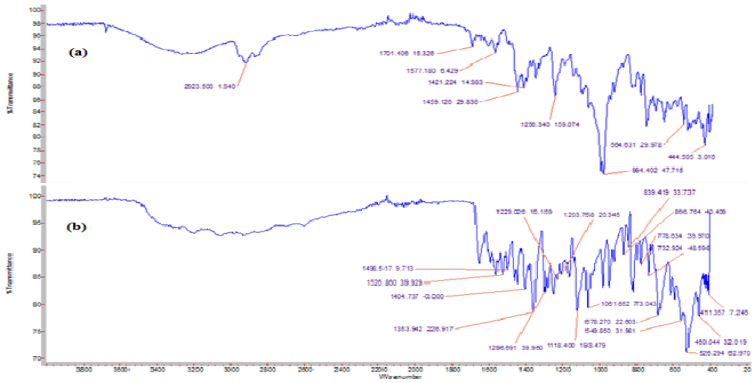
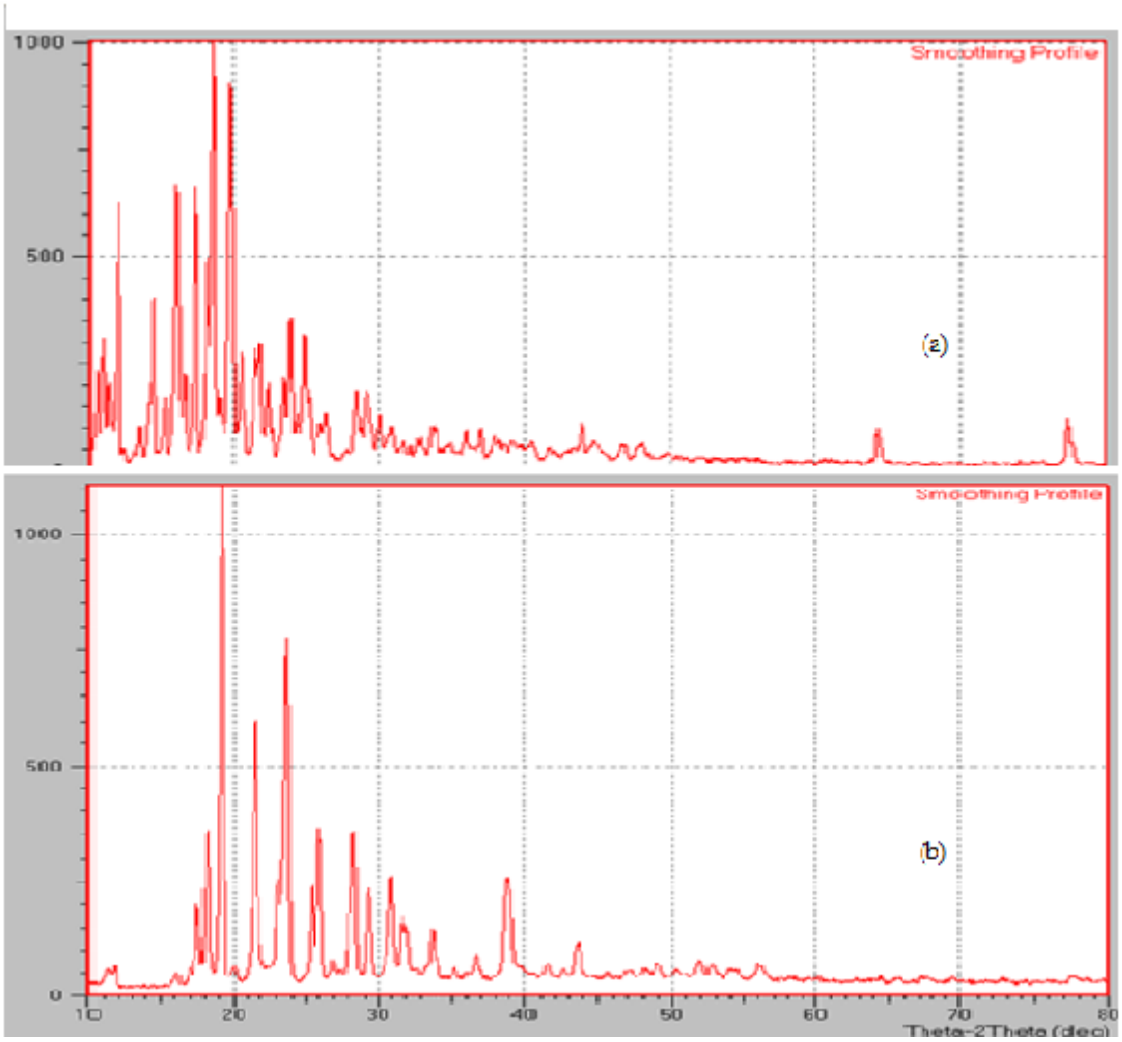


Figure 3. FTIR spectrum ofDexlansoprazole –PVP crystals (a) and pureDexlansoprazole (b)

DISCUSSION:

From the fig 3 FTIR patterns of pureDexlansoprazole(b)shows characteristic absorption at 1456 C-H stretching of methyl groups, 1353 of S=O stretching of sulfinylgroup, 1296 of C-N stretching for aromatic amine. But there is a change in the functional groups present in the prepared crystals (a) compared to that of pureDexlansoprazole drug, absorption at 2923 of C-H stretching of alkanes, 1701 of C=O stretching of conjugated acids,1421 O-H stretching of alcoholic group, 1459 C-H stretching of methyl groups, 1256 stretching of C-O aromatic esters showing presence of new bond formation in the optimized crystals. But it confirms no formation of hydrogen bonding between drug and the co-former. Thus it formed a new form of crystal lattice.

Powder X-Ray Diffraction



CONCLUSION:

TheDexlansoprazole-PVP optimized crystals were preparedsuccessfully using co-former PVP, magnesium chloride as basic compound by anti- solvent addition method. These crystals were analytically characterized by melting point, FTIR, DSC and XRD. Results of studies reveals that formation of new crystal phases due to physical and chemical interactions between API and co-former, but by the FTIR results it was confirmed that there is no formation of co-crystals. Prepared crystals showed better solubility, dissolution and micromeritic properties as compared to pureDexlansoprazole. By the stability studies it can be concluded that at 25 ºC ±2C / 60% condition have good stability than the 40 ± 2 ºC/ 75% RH ± 5% RH. Many attempts were made to produce a stable, novel crystalline form ofDexlansoprazole to overcome all the major drawbacks of drug, but it failed in preparation of cocrystalsby a novel particle engineering technique: cocrystallization. Further investigations were on progress to produce at most best formulation.

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