International Journal of Engineering Research & Management Technology
(Peer-Reviewed, Open Access, Fully Refereed International Journal) ISSN: 2348-4039
Volume 11, Issue-1 January-February- 2024 Impact Factor: 7.09
Email: editor@ijermt.org www.ijermt.org

Physicochemical Properties of Poorly Soluble Dexlansoprazole by Co-crystallization Techniques - *In vivo* Studies

Sunil Kothari
Research Scholar, School of Pharmacy,
Glocal University,Mirzapur Pole, Saharanpur (U.P) India.

Prof. (Dr.) Ravindra Rohidas Patil
Research Supervisor, School of Pharmacy
Glocal University Mirzapur Pole, Saharanpur (U.P)

Abstract-:
To overcome the poor solubility and low bioavailability of Dexlansoprazole co-crystallization was attempted. Dexlansoprazole co-crystals were prepared with selected co-former gallic acid by co-grinding method. Characterization was carried out through X-ray diffraction, Fourier Transform infra-red spectroscopy, differential scanning colorimetry and scanning electron microscopy. The Fourier-transform infrared spectroscopy results showed that a hydrogen bond was formed between Dexlansoprazole and gallic acid to yield a co-crystal.Micrometric properties, solubility, dissolution studies, pre-compression and post-compression properties were evaluated. Dexlansoprazole co-crystals were formulated into conventional tablets. In vivo and stability studies were performed. Pharmacokinetic parameters and dynamic studies of the formulation were statistically analysed and a value of $p<0.05$ was considered to be significant. Thus physicochemical properties and bioavailability of Dexlansoprazole was improved through co-crystallization.
Key words: Co-crystallization, micromeritic properties, bioavailability, Dexlansoprazole,

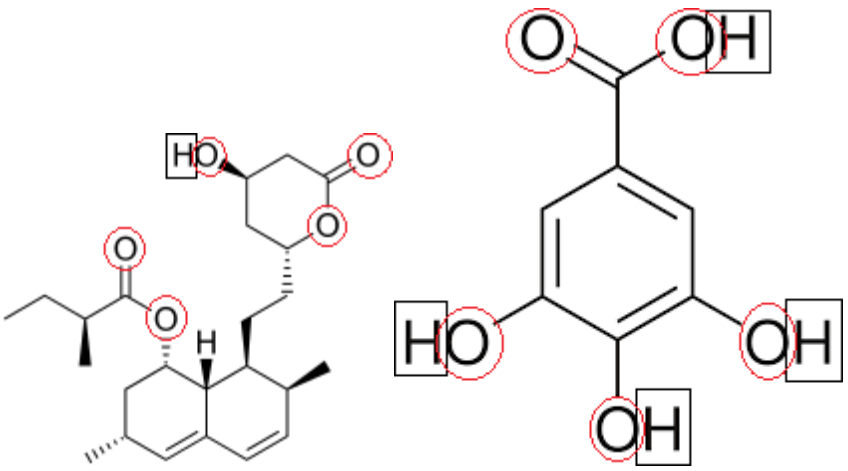
INTRODUCTION-:

For pharmaceutical product development the main issues faced are stability, solubility, bioavailabilityand material properties of active pharmaceutical ingredients (API)[1]. Crystals are prioritized in pharmaceutical industry because of their greater stability and reproducibility compared to amorphous and other solids such as partially crystalline forms, sub-cooled liquid and different types of crystal forms with variable dissolution rates and intrinsic solubilities, which severely impact bioavailability [2-4]. Rapid growth has been reported in the design and synthesis of multi-component crystal systems [5]. Co-crystals are defined as crystalline complexes

of two or more neutral molecular constituents bound together in a crystal lattice through non-covalent interactions, primarily hydrogen bonding [6]. Co-crystallization is an authentic method to alter the major properties of drugs such as solubility, dissolution rate, stability, hygroscopicity, photosensitivity, thermo sensitivity, flowability and compressibility without altering pharmacological properties[5,7]. The formation of a co-crystal involves an API and a pharmaceutically acceptablemolecule known as co-former. The resulting multicomponent crystalline phasemaintains the intrinsic activity of the parentAPI[8]. Co-former incorporated in co-crystallization process may be from various food additives, preservatives and pharmaceutical excipients or could even be another drug[9,10] but they must be GRAS (generally recognized as safe) substances. Various forms of API such as salts, amorphous, solvates, polymorphs and inclusion complexes were produced for enhancing solubility, but all of these have some limitations in their utility[11,12]. Co-crystals are non ionizable, non-salt form of modified drug substances with better enhancement in physicochemical properties with no limitations in their utility.In co-crystal development one of the approaches of co-former selection is based on trial and error. Other approaches are supramolecularsynthon approach which utilizes Cambridge Structural Database (CSD)to effectively prioritize co-formers for crystal form screening, Hansen solubility parameter and knowledge of hydrogen bonding between co-former and API[15,16]. With knowledge of hydrogen bond donors and acceptor groups of both Dexlansoprazole and gallic acid according to the CSD, Hansen solubility parameter, an attempt to form co-crystals of Dexlansoprazole was successful.

MATERIALS AND METHODS

Dexlansoprazole was obtained as a gift sample from Beijing HWRK Chemicals Ltd., China, and gallic acid (Extra pure) was purchased from Molychem, Mumbai, India.



(A) (B)

Fig. 1: Representation of hydrogen bond donars and acceptors Representation of hydrogen bond donars and acceptors of (A) Dexlansoprazole and (B) gallic acid. Circles indicate acceptor groups and rectangles indicate donar groups.

Preparation of standard curve in pH 6.8 phosphate buffer:

One hundred milligrams of Dexlansoprazole was dissolved in 5 ml of methanol in a volumetric flask, made up to100 ml with pH 6.8 phosphate buffer. From this primarystock 10 ml was withdrawn and transferred to another volumetric flask, and the volume was made up to 100 ml with pH 6.8 phosphate buffer. From this secondary stock solution, different volumes were taken in 10 ml volumetric flasks, the final volume was made up to 10 ml in each flask with pH 6.8 phosphatebuffer, to obtain 5, 10, 15, 20, 25 and 30 µg/ml concentrations. The absorbance was measured at 236 nm on a UV spectrophotometer [17].

Attempts to prepare Dexlansoprazole co-crystals:

To prepare Dexlansoprazole co-crystals, the 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. Firstly the most suitable co-former was selected by trial and error using the basic method of co-grinding. Taking solubility as the main criteria, the co-former which produces greater solubility of Dexlansoprazole is selected. For optimizing the concentration of the co-former and a method of preparation, solvent drop grinding, slurry crystallization, slow evaporation, anti-solvent addition methods were attempted. Finally gallic acid was selected and the method of preparation chosen was the co-grinding method (Table 1).

Preparation of Dexlansoprazole co-crystals by co-grinding method:

Pharmaceutical Dexlansoprazole co-crystals were prepared with gallic acid and Dexlansoprazole in 1:1 molar ratio using the co-grinding method. Dexlansoprazole and gallic acid were pre milled separately for 15 mins, equimolar quantity of these were added to mortar, ground continuously for 45 min in a mechanical grinder. The powder was then scratched from walls of mortar and dried at 40 and stored in a vial.

Melting point of prepared Dexlansoprazole co-crystals:

Melting point of pure Dexlansoprazole, co-formers and cocrystals were obtained using the capillary method in liquid paraffin. The capillary filled with drug powder was placed in a melting point apparatus and the liquid paraffin was heated, melting point of drug powder was noted when it melted in the capillary.

Scanning electron microscopy (SEM):

The morphology of the co-crystals was examined under the SEM equipped with an energy dispersive X-ray (EDX). The samples were covered with carbon coating in order to increase conductivity of the electron beam. Operating conditions were accelerating voltage 15 KV current 87000nA.

Differential scanning calorimetry (DSC):

Thermal analysis of Dexlansoprazole and prepared Dexlansoprazole co-crystals were recorded individually on a DSC(Q200 Waters). The samples were scanned at 10°/min over a temperature range of 50- 300º with nitrogen gas in an aluminium pan.

Fourier transform infrared (FT-IR) studies:

FT-IR spectra of pure Dexlansoprazole and prepared cocrystals were recorded individually on a PerkinElmer FTIR spectrophotometer by mixing them with potassium bromide. Scans were recorded in the range of 400-4000 cm-1.

Powder X-ray diffraction (XRD):

Powder XRD was performed at room temperature with an X-ray diffractometer. Monochromatic

Cu radiation was obtained with a Ni-filtration and a system of diverging and receiving slides of 1.0º and 0.3 mm, respectively. The diffraction pattern was measured with a voltage of 40 kV and current of 30 mAover a 2θ range of 10-80º using a sampling pitch of 0.02º with a scan speed of 4º/min.

Drug solubility study:

An excess quantity of co-crystals was added to 10 ml of distilled water, sealed, protected from light and placed in a shaker for 48 h. After equilibrium was attained, the contents of the flask was filtered through a 0.45 µm Millipore filter. The filtrate was diluted to 100 ml with distilled water and the content of Dexlansoprazole was estimated on a UV spectrophotometer at 236 nm.Dexlansoprazole content in the filtratewas calculated from the UV absorption value and solubility is calculated using a calibration curve[18] using the formula, concentration.

Drug dissolution study:

A dissolution study was carried out for Dexlansoprazole and prepared co-crystals using USP type I (basket type) dissolution aparatus with 900 ml of pH 6.8 phosphate buffer as the dissolution medium at 37±0.5°. Samples were withdrawn at definite time intervals (10 min) for 1 h and each time fresh dissolution medium was added to replace the volume sampled and the samples were quantified using a UV spectrophotometer at 236 nm[17].

Micromeritic properties:

Angle of repose for Dexlansoprazole and Dexlansoprazolecocrystals was determined using the fixed funnel method. Accurately weighed Dexlansoprazole and co-crystals were taken in a funnel. The height of the funnel wasadjusted in such a way that the tip of the funnel just touched the apex of the heap of the powder. The powder was allowed to drift through the funnel freely to the bottom. The height and diameter of the powder

cone was measured and angle of repose was calculated[17]. Tan θ=h/r, where, θ is the angle of repose, h is the height in cm, r is the radius in cm, Angle of repose 25-30 represented excellent flow properties, 31-35 represented good flow properties, 36-40 indicated fair flow properties, 41-45 showed passable flow properties.

Bulk density and tapped density:

Bulk density and tapped density were determined with the aid of the bulk density apparatus. Apparent bulk density was determined by pouring the blend into a graduated cylinder. The bulk volume (V_b) and weight of the powder (M) was determined [17]. The bulk density was calculated using the formula, $D_b=M/V_b$, where, M is the mass, $V_b$is bulk volume. The measuring cylinder of the apparatus was filled with a known mass of blend and was tapped for a fixed period time. The minimum volume (V_t) occupied in the cylinder and the weight (M) of the blend was measured [17]. The tapped density was calculated using the formula, $D_t=M/V_t$, where, M is the mass and $V_t$is the tapped volume.

Hausner's ratio:

It is a divergent index of powder flow. It is calculated using the formula, Hausner's ratio= tapped density(ρt)/ bulk density (ρb), Lower Hausner's ratio (<1.25) indicated better flow properties than higher rations.Ratios between 1.25 to 1.5 reflected moderate flowproperties and more than 1.5 indicated poor flow[17].

Tablets preparation, direct compression:

Direct compression method was used for preparing Dexlansoprazoletablets.Mainadvantages of direct compression are low manufacturing cost and high mechanical integrity of the tablet. Dexlansoprazole co-crystals and other ingredients were initially added to a clean mortar. By continuous mixing of all ingredients for 10 min in a mortar to produce geometrical distribution of drug in the bulk powder. Final mixture was compressed on a tablet punching machine, using the manual hydraulic press at constant pressure. The composition of the compressed tablets is as follows, Dexlansoprazole 60 mg, microcrystalline cellulose 70 mg, lactose 130 mg, starch (5%)- 15 mg and magnesium stearate (1.5%) – 5 mg.

Tablet evaluation, weight variation and hardness:

Pre-compression properties are the micromeritic properties of formulations such as angle of repose, bulk density, tapped density, Carr's index, and Hausner'sratio[17], the determination of which was alreadydescribed. Post-compression properties includedthe weight variation test, which was performed asfollows. Twenty tablets were randomly selected,weighed individually and all together in an electronicbalance[20]. The average weight of 20 tables wascalculated and weight variation was calculated. Weightvariation=average weight-weight of each tablet/average

weight ×100. The thickness and diameter of tabletswere determined in mm using Verniercallipers. Randomly 5 tablets were selected, average thickness and diameters were determined. Hardness of tablets was measured.

Friability test:

The friability of tablets was measured in a Roche friabilator with 20 tablets randomly selected were weighed to obtain initial weight (W1) followed by placing these tablets in the friabilator and subjected to 100 revolutions after which the final weight (W2) of 20 tablets was weighed. The percent weight loss was calculated as, % friability=(W1−W2)/W1)×100. The% friability should be preferably between 0.5 and 1.0%.

Disintegration test:

Six tablets were randomly selected and placed in the glass tubes of a USP disintegration test apparatus.Distilled water was used as the disintegrating medium,the bath temperature was maintained at 37±2º, and 30 cycles/min of movement frequency was adjusted.

The tablets were observed for 30 min to see if any residue is left in the glass tubes and the time taken for the tablets to disintegrate was noted.

Comparative *in vitro* drug release study[17,21,22]:

Drug release studies with pure Dexlansoprazole, Dexlansoprazoleco-crystal tablets and marketed tablets were carried out in a USP dissolution apparatus type I set at 50 rpm with 900 ml of pH 6.8 phosphate buffer maintained at 37±0.5º as the dissolution medium. At specific time intervals up to 1 h, sampleswere withdrawn for analysis at 236 nm on a UV spectrophotometer against pH

6.8 Phosphate buffer as blank. Each withdrawn sample volume was replaced with an equal volume of freshpH6.8 phosphate buffer to maintain sink conditions.

Stability studies of Dexlansoprazole co-crystal tablets:

Stability studies of the optimized DexlansoprazoleCocrystalstablets were performed under the conditions of 40±2º/75±5 % relative humidity and 25±2º/60 ±5 % relative humidity for a period of 90 d. Tablets were analysed for physical appearance, solubility and dissolution[23,24].

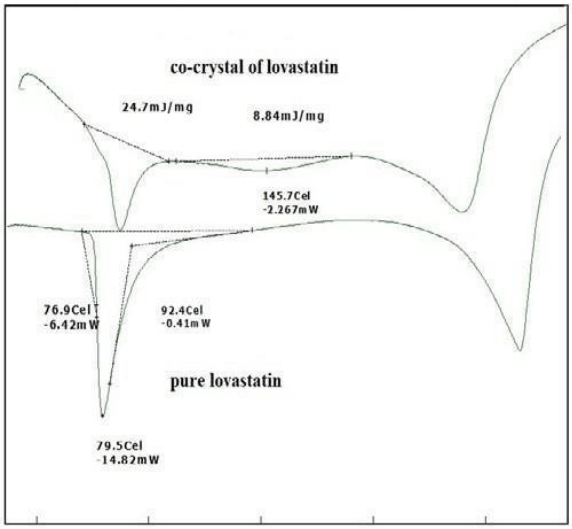
RESULTS AND DISCUSSION

Solubility and melting point data of different preparations were presented in Table 2. LG1 coded preparation showed enhanced solubilitywhen compared with pure Dexlansoprazole. Although some of the other preparations showed greater solubility enhancement than LG1, these were not chosen for further studies due to the fact that the ratio of gallic acid and Dexlansoprazole led to bulky size, which would produce problems to formulate and obtain patient acceptance. Melting point is one of themost important physicochemical properties of co-crystals and considered as the preliminary test for confirmation of changes occurred in free drug. When the co-crystals were formed the melting point must lie in between the melting points of the two individual molecules, but either below or above the melting point of the drug. If such results are obtained, it would serve as a confirmation that the co-crystals have formed[6].

It was found that the melting point of preparation was 165°, which was different from the melting points of Dexlansoprazole (178°) and the co-former gallic acid (260°) confirming the formation of co-crystals with some chemical interaction between both molecules[9].

From the DSC thermograms (fig. 2), it was observed that the prepared co-crystals were different in pattern and intensity, from that of Dexlansoprazole indicating the formation of a chemical bond. The shift in the melting point is due to the change in crystal arrangement of the Dexlansoprazole with gallic acid, forming a relatively different crystal lattice leading to co-crystal formation. Pure Dexlansoprazole curve showed sharp melting peak at 79.5º while co-crystal curve showed a large broader peak at 145.7º, these changes occurred on the account of interaction induced byweak cohesive forces and bonded together by reversible hydrogen bonding, suggesting.

Code	Co-crystalcomponents	Ratioofdrug:Co-former	Methodofpreparation	Meltingpoint(°)	Solubility(mg/ml)
LG1*	Dexlansoprazole+gallic acid	1:1	Co-grinding	165	0.248*
LG2	Dexlansoprazole+gallic acid	1:2	Co-grinding	168	0.264
LG3	Dexlansoprazole+gallic acid	1:3	Co-grinding	163	0.281
LG4	Dexlansoprazole+gallic acid	1:4	Co-grinding	160	0.261
LG5	Dexlansoprazole+gallic acid	1:5	Co-grinding	250	0.255
LG6	Dexlansoprazole+gallic acid	1:1	Solventdropgrinding	165	0.146
LG7	Dexlansoprazole+gallic acid	1:1	Slowevaporation	105	0.119
LG8	Dexlansoprazole+gallic acid	1:1	Antisolventaddition	103	0.005
LG9	Dexlansoprazole+gallic acid	1:1	Slurrycrystallization	125	0.152
PL	PureDexlansoprazole			178	0.0024



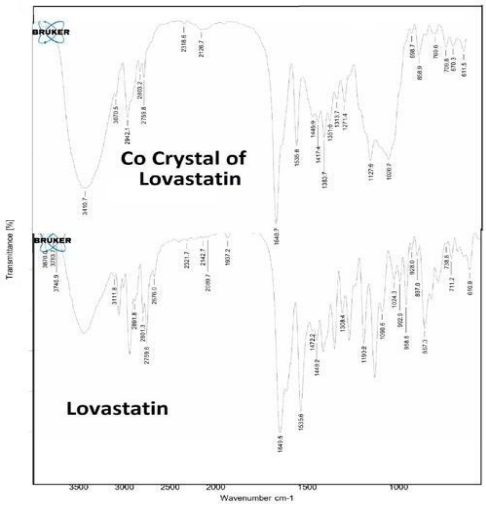


Fig. 2: DSC curves of co-crystal Dexlansoprazole and pure Dexlansoprazole Fig. 3: FTIR spectra of pure Dexlansoprazole and Dexlansoprazole co

-crystals

The formation of co-crystals. The FTIR spectrum of pure Dexlansoprazole (fig. 3) showed characteristic absorption peaks at 3746.9 (O-H stretching of free alcohol), 2801.3 and 2759.6 (O-H stretching of intramolecular bonding of alcoholic group), 1649.5 (C=C stretching for conjugated alkenes), 1448.2 (C-H bending of methyl group in alkane), 1308.4 (C-O stretching of ester). But spectrum of Dexlansoprazole co-crystals showed additional absorption peaks at 3410.7, 1127.6 and 1026.7, which indicated theO-Hstretching of intermolecular hydrogen bonding, C-O stretching of secondary alcohol due to formation of hydrogen bonding between Dexlansoprazole and gallic acid. This served as the evidence for hydrogen bonding between Dexlansoprazole and gallic acid, leading to co-crystals. XRD is one of the most important characteristics for identification of interactions between the components. A different XRD pattern of co-crystals from Dexlansoprazole confirmed the interaction between them[27]. The crystallogram patterns in fig. 4 clearly showed sharp distinct peaks, which were at different 2θ value with different intensities in each crystallogram, however some of the 2θ values of pure Dexlansoprazole disappeared in the co-crystal crystallogram.

It confirmed the formation of co-crystals by hydrogen bonding between Dexlansoprazole and gallic acid with different new crystal habitat. In addition, there was a decrease in the degree of crystalinity of Dexlansoprazole that might have occurred due to the bonding of Dexlansoprazole with the co-former resulting in the formation of Dexlansoprazole co-crystals. SEM images in fig. 5 of pure Dexlansoprazole and Dexlansoprazole co-crystals clearly showed that there was a change in the size and shape duemostly.

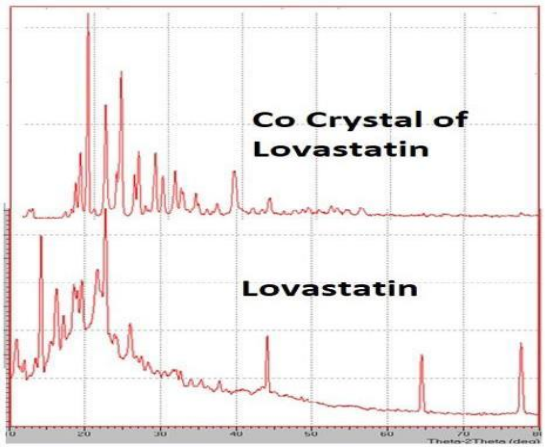


Fig. 4: XRD patterns of pure Dexlansoprazole and Dexlansoprazole co-crystals

Properties	F1	F2	F3	F4	F5	F6
Bulkdensity (mg/ml)	292±1.1	293±1.3	290±1.5	290±1.8	295±1.3	295±1.3
Tappeddensity(mg/ml)	345±1.2	344±1.1	340±1.3	344±1.5	359±1.6	359±1.8
Angleofrepose(°)	24±1	25±2	26±1.1	27±1	29±1.2	29±1.4
Carr'sindex(%)	15.3±0.3	14.8±0.4	14.7±0.5	15.6±0.2	17.8±0.5	17.8±0.3
Hausner`sratio	1.18±0.02	1.17±0.01	1.17±0.02	1.18±0.06	1.21±0.02	1.21±0.03
Hardness(kg/cm^2)	4.6±0.8	4.7±0.5	4.6±0.6	4.8±0.4	4.9±0.4	4.9±0.3
Thickness(mm)	3.6±0.2	3.5±0.4	3.6±0.2	3.4±0.3	3.6±0.2	3.6±0.2
Friability(%)	0.77±0.02	0.65±0.05	0.75±0.03	0.7±0.01	0.63±0.03	0.72±0.02
Disintegrationtime(sec)	225±2	205±3	190±2	184±3	154±4	158±2
Weightvariation(mg)	277±2	276±2.6	275±2	277±2	275±1.6	261±1.5
%Drug releasefor1h	43.55	44.66	46.15	50.23	55.35	4.22

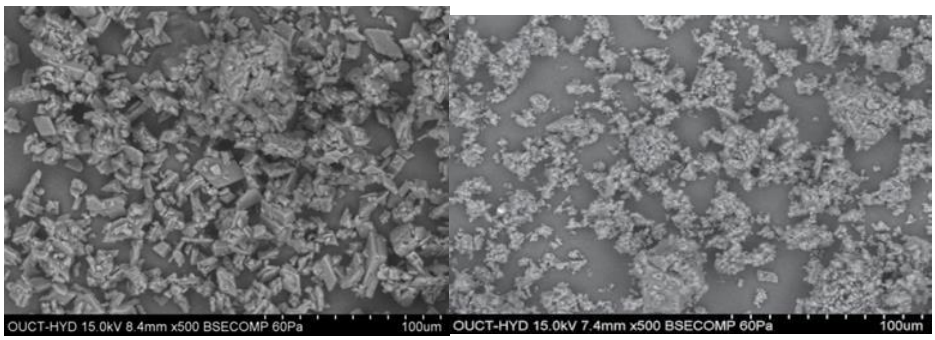


Fig. 5: SEM pictomicrographs of Dexlansoprazole and Dexlansoprazolecocrystals SEM pictomicrographs of image (A) pure Dexlansoprazole and image (B) Dexlansoprazole co-crystals

to bonding by the gallic acid crystals as shown in theimage B, which is distinct from image A, indication the formation of Dexlansoprazole co-crystals. Saturation solubility of Dexlansoprazole co-crystals was 0.248 mg/ml which is 100 timesmore than the solubility of Dexlansoprazole0.0024 mg/ml. Table 3 showed the pre-compression and post-compression properties which were within the limits of USP guidelines. Fig. 6 in which *in vitro*dissolution profiles of formulations were shown, F5 (co-crystal formulation) showed prominent increase in percent drug release as compared to pure Dexlansoprazoleformulation (F6) and marketed tablets. Stability studies of optimized Dexlansoprazoleco-crystal tablets (F5) under 2 different conditions were carried out for 90 days, the results of which were shown in Table 4. These studies indicated that there were no significant changes in the physical parameters, post compression properties and % drug release during 60 min, after storing under temperature and humidity condition of 25±2º/60±5 % relative humidity. However storage under temperature and humidity condition of 40±2º/ 75±5 % relative humidity showed slight decreased in percent drugreleased within 60 min.

CONCLUSION

Characterization was carried out through X-ray diffraction, Fourier Transform infra-red spectroscopy, differential scanning colorimetry and scanning electron microscopy. The Fourier-transform infrared spectroscopy results showed that a hydrogen bond was formed between Dexlansoprazole and gallic acid to yield a co-crystal.Micrometric properties, solubility, dissolution studies, pre-compression and post-compression properties were evaluated. Dexlansoprazole co-crystals were formulated into conventional tablets. In vivo and stability studies were performed. Pharmacokinetic parameters and dynamic studies of the formulation were statistically analysed and a value of $p<0.05$ was considered to be significant. Thus physicochemical properties and bioavailability of Dexlansoprazole was improved through co-crystallization.

REFERENCES

1. DhumalRS,KellyAL,YorkP, CoatesPD,ParadkarA.Cocrystalization and Simultaneous Agglomeration Using HotMeltExtrusion.PharmRes2010;(12):2725-33.
2. ShanN,ZaworotkoMJ.Theroleofcocrystalsinpharmaceuticalscience.Drug DiscoveryToday 13;(9-10):440-6.
3. Sohrab R. Applications of the crystallization process in thepharmaceuticalindustry. FrontChemEng2010;4(1):2-9.
4. Desale PK. A novel method: Co-crystallisation. Int J PharmaInven2013;3:4-9.
5. AlmarssonO,ZaworotkoMJ.Crystalengineeringofthecomposition of pharmaceutical phases. Do pharmaceutical co-crystals represent a new path to improved medicines?.ChemCommun2004;(17):1889-6.
6. JayasankarA,SomwangthanarojA,ShaoZJ,Rodrıguez-HornedoN.Co-crystalformationduringcogrindingandstorageismediatedbyamorphousphase.PharmRes2006;23:2381-92.
7. SchultheissN,NewmanA.PharmaceuticalCocrystalsandtheirphysicochemical properties. Cryst Growth Des 2009;9:2950-67.
8. Vishweshwar P, McMahon JA, BisJA, Zawworotko MJ.Pharmaceuticalco-crystals.JPharmSci2006;95:499-516.
9. Rodriguez-HornedoN,NehmSJ,JayasankarA.Cocrystals:design, properties and formation mechanisms, InEncyclopediaofPharmaceuticalTechnology,3rded.Taylor&Francis,London, 2007.p.615-35.
11. Mathew D. A study of suitability of nimesulidebetacyclodextrincomplexin oral and topical dosage forms. IntJ Pharm Pharm Sci. 2009;(1):193-8.
12. Srikanth MV, Babu GVMM, Rao NS, Sunil SA, BalajiS, Ramanamurthy KV. Dissolution rate enhancement of poorly soluble bicalutamide using β-cyclodextrin inclusion complexation.Int J Pharm PharmSci2010;(2):191-8.

13. Babu JN, Nangia A. Solubility Advantage of Amorphous Drugs and Pharmaceutical Cocrystals. *Cryst Growth Des*2011;11(7):2662-79.
14. Bakhle SS. Development and Evaluation of Liquid and Solid Self-microemulsifying Drug Delivery System of Dexlansoprazole. Asian J PharmaSci 2016;10(1):22.
15. Sulbha RF, Milind PW, Shilpi R. Coformer selection: an important tool in cocrystal formation. Int J Pharm PharmSci2014;6:9-14.
16. Aravind RS, Swati SR, Nandkishor NJ. Insights of Dosage form Design: Polymorphs and Co-crystals. Asian J Biomed Pharm Sci2013;(27):1-8.
17. Divyabharathi Y, Rajesh VB. Enhancement solubility of Dexlansoprazole drug by using liqui-solid technique. World J Pharm Res 2012;17:567-87.
18. Chandel N, Gupta V, PandeyA, Saxena S, SheetalChoudhary. Co-crystalization of aceclofenac and paracetamol and their Characterization.Int J Pharm Life Sci 2011;2(8):1020-8.
19. Chatwal GK, Anand SK. Instrumental methods of chemical analysis. 5th ed. Mumbai, Himalaya publishing house; 2006.
20. Prakash O, Saraf S, Rahman M, Agnihotri N, Pathak VK. Formulation and Evaluation of Floating Nateglinide Tablets Using Factorial Design.RRJoPS 2013;2(4):13-9.
21. Dupinder K, Seema S. Development and characterization of Dexlansoprazole loaded microspheres. Int Res J PharmAppSci 2013; 3(5):197-205.
22. Viswanath V, Somasekhar G. Stability enhancement of Dexlansoprazole by liquisolid compaction technique. J Glob TrenPharmaSci 2014;5(3):1933-39.
23. Anand DSS, Sultana SS, Sultana SS, Ramana BV, Nagarajan G. Formulation and evaluation of bilayer floating tablets of simvastatin and Dexlansoprazole. J ChemPharma Res 2014:6(12):186-97.