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Crystal Transition and Drug-excipient Compatibility of the Clarithromycin in Sustained Release Tablets

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Abstract: Background: Clarithromycin is widely used for infections of helicobacter pylori. It shows polymorphic. Crystalline state changes of clarithromycin in sustained release tablets was found.

Objective: To find the influential factor of the crystal transition of clarithromycin in preparation process of sustained release tablets and to investigate the possible interactions between the clarithromycin and pharmaceutical excipients.

Method and Results: The crystal transition of active pharmaceuticals ingredients from form Ⅱ to form I in portion in clarithromycin sustained release tablets were confirmed by x-ray powder diffraction. The techniques including differential scanning calorimetry and infrared spectroscopy, x-ray powder diffraction were used for assessing the compatibility between clarithromycin and several excipients as: magnesium stearate, lactose, sodium carboxymethyl cellulose, polyvinyl-pyrrolidone K-30 and microcrystalline cellulose. All of these methods showed compatibilities between clarithromycin and the selected excipients. Alcohol prescription simulation was also done, which showed incompatibility between clarithromycin and concentration alcohol.

Conclusion: The reason of crystal transition that clarithromycin incompatibility with not less than 85% concentration alcohol was confirmed.

Keywords: clarithromycin; compatibility; differential scanning calorimetry; x-ray powder diffraction; infrared spectroscopy.

1. INTRODUCTION

Clarithromycin (CAM) is a semisynthetic macrolide antibiotic, which exhibits excellent activity against gram-positive bacteria, some gram-negative bacteria, anaerobic bacteria, mycoplasma and chlamydia[1]. As first-line drug, doctors use CAM with proton pump inhibitor to eradicate helicobacter pylori, it showed high potential for application as a mono-therapy in vivo[2]. CAM is stable under acidic conditions and is well absorbed from the gastrointestinal tract. Eight polymorphic forms of CAM were previous reported and their crystal structure were determined, form 0[3], form I[4], form II[5], form III[6], form IV[7], form V[8], hydrochloride salt[9] and methanol solvate[10]. The dissolution rate of CAM is affected by polymorphic transitions. Form I of CAM has an intrinsic rate of dissolution about three times that of crystal form II, and under acidic conditions containing hydrochloride, form II transforms to a chloride salt form with a higher dissolution rate[11].

Pharmaceutical dosage forms contain both active pharmaceuticals ingredients (API) and inactive materials called excipients. In theory, excipients are pharmacologically inert, but they can interact with API in the dosage form. The behavior of the dosage form was dependent on process variables and the interrelationship between the various excipients and their impact on the API. Certain physical changes as polymorphic conversion or change from crystalline to amorphous form may also occur in drug-excipient mixtures. Therefore, compatibility studies using thermal techniques must perform to accelerate the development of a suitable drug for macrolide antibiotic. The compatibilities between the API and excipients can affect stability, dissolution and bioavailability of the drug and thereby, hinder its therapeutic efficacy and overall effectiveness[12-13].

Throughout the different techniques reported on drug-excipient compatibility studies, differential scanning calorimetry (DSC) has proven to be a well-established method. DSC represents a leading thermal analysis technique that has been used for over 50 years. Appearance, shift, disappearance of peaks or variations in the corresponding enthalpy of transition are interpreted as an indication of interaction and possible incompatibility[14]. Other

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complementary techniques as infrared spectroscopy (FT-IR) or x-ray powder diffraction (XRPD) can be useful in avoiding misleading conclusions[15]. FT-IR is sensitive to the structure and environment of organic compounds, any potential interactions causing hydrate formation, dehydration or polymorphic changes can easily be detected[16]. XRPD is helpful to evaluate drug-excipient compatibility especially during compression and granulation producer, due to the unique set of diffraction peaks of a dosage form[17].

This paper reported the use of XRPD to confirm the crystal form of API and API in CAM sustained release tablets. This study was also undertaken to evaluate the thermal stability of CAM and the impact of excipients used in the solid dosage forms when combined in binary mixtures. In addition, compatibility of alcohol with CAM was also studied by XRPD and DSC.

2. MATERIALS AND METHODS

2.1 Materials

CAM active pharmaceutical ingredient (API) (not less than 99% purity) and a total of 10 samples of sustained release tablets were collected from 2 pharmaceutical Co., Ltd. in China, locations including Laiyang (LY), Hainan (HN), respectively. The blank excipient were also supplied from the 2 pharmaceutical Co., Ltd.. Magnesium stearate (MGST), lactose, sodium carboxymethyl cellulose(CMC), polyvinyl-pyrrolidone K-30 (PVP K-30), microcrystalline cellulose (MCC) were supplied by Sinopharm Chemical Reagent Co., Ltd (China). In this study, the binary mixtures (BMs) 1:1 (w/w) of CAM with the individual excipient have been prepared using a mortar and pestle, grinding the mixture for 5 min each.

2.2 Instrument and methods

2.2.1 DSC

The DSC curves of CAM and BM were obtained using a TA Q2000 scanning calorimeter, under nitrogen flow of 50 mL min^{-1} with heating rate of 10 ℃min-1, in the 40-250℃ temperature range. The DSC instrument was calibrated using indium as standards.

2.2.2 FT-IR

FT-IR spectra of drug, excipients and grinding mixtures were recorded on a Nicolet Spectrum 6700 using KBr stressed discs in the range of 4000-400 cm^{-1}, the result was obtained by combining the 32 scans.

2.2.3 XRPD

The x-ray powder diffraction was performed on a Bruker D8 advance diffractometer using a copper anode. The analytical angle intervals of 2θ are in the range of 3-40°, and the scanning speed is 0.02 ° s^{-1}. The samples were prepared on a glass slides with a thin layer of powder.

3. RESULTS

3.1 The crystal form of API and API in CAM sustained release tablets

The x-ray diffraction patterns of the API of LY and HN indicated that the crystal form of them were regarded as form Ⅱ[5]. However, the CAM sustained release tablets of LY contained the form Ⅱ, tablets of HN contained the form I and form Ⅱ.

3.2 Compatibility study of clarithromycin and pharmaceutical excipients

3.2.1 DSC results

In our study, we showed the main thermal events for CAM and BMs by using DSC analysis, selected DSC scans of the drug and drug-excipient mixtures are shown in Fig.1~ Fig.5, thermal behavior of API, respective excipient, and the BMs were compared in the curves. The peak temperature (Tpeak), the initial melting temperature (Tonset), and heat of fusion or enthalpy (△H) of CAM in five excipient mixtures are summarized in Table 1.

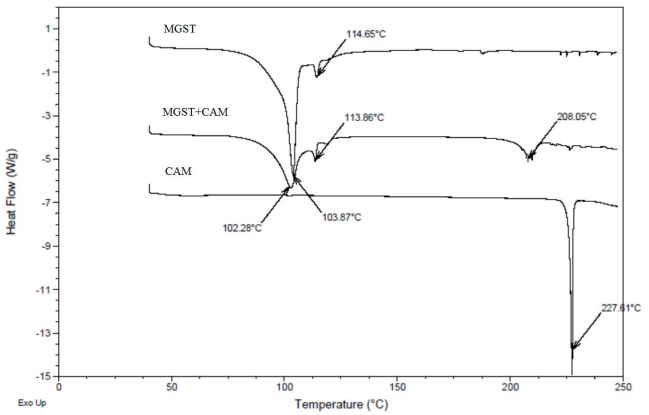

Fig. 1 The DSC curves of BM of CAM - MGST

The DSC curves of CAM showed a sharp endothermic peak at 227.61 ℃ which is its melting temperature. According to previous research, the melting temperature of drug would not change, but the peak temperature and peak shape would slightly change in the BMs[18], so these minor changes may not be enough proof to indicate the interaction between drug and excipient.

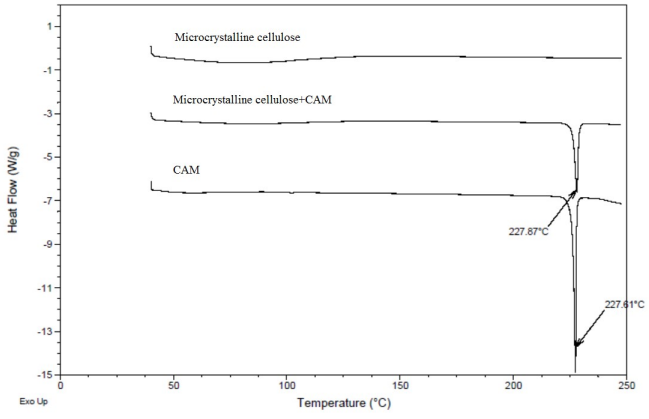

Fig. 2 The DSC curves of BM of CAM - MCC

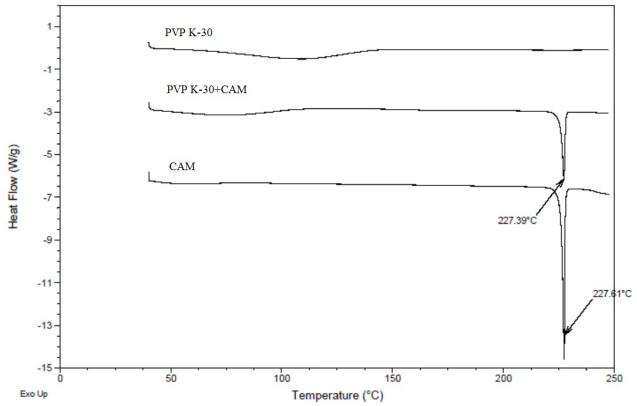

Fig. 3 The DSC curves of BM of CAM - PVP K-30

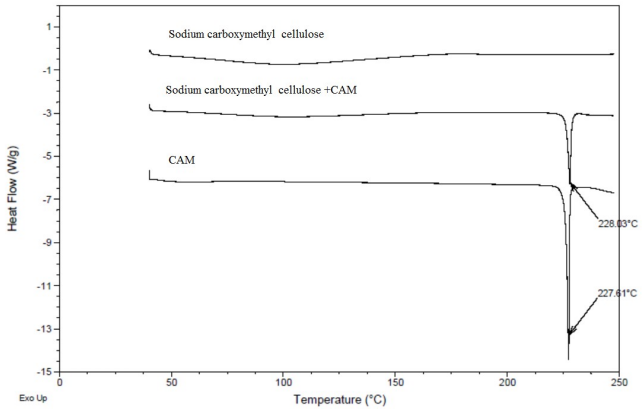

Fig. 4 The DSC curves of BM of CAM - CMC

In the DSC curve of MGST, one endothermic peak was seen at 103.87℃ and another one at 114.65℃, the results were complied with previous research, and expected due to loss of water and impurity of palmitate[19]. The absence of the melting peak of CAM can be explained by the possible dissolution of CAM in the melted stearate (melting point 110 ℃).

The DSC curve of MCC shows in the BMs curve, the sharp peak at 227.87℃ is the characteristic peak of CAM, and the △H value is 39.08 J/g which indicate there was no interaction between drug and excipient. The same happened with the curve of CMC and PVP K-30.

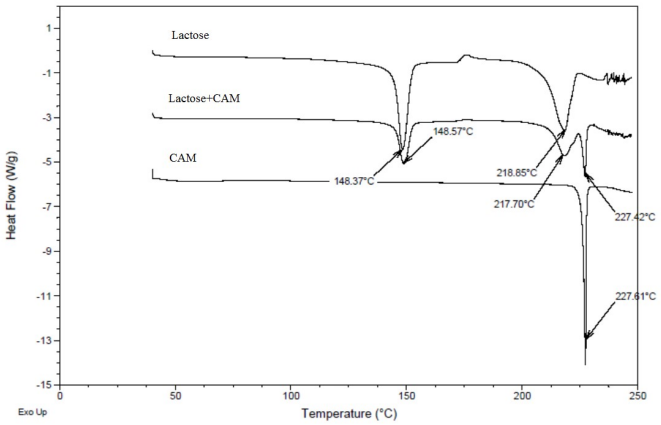

Fig. 5 The DSC curves of BM of CAM - lactose

Table 1. Initial temperature, peak temperature of the melting event and variation in the enthalpy of CAM and BM

Sample	TONSET/℃	Tpeak/℃	ΔH/J˙g-1
CAM	226.32	227.40	62.46
MGST+CAM	207.62	207.96	28.96
Lactose+CAM	225.59	227.29	20.98
PVP K-30+CAM	225.87	227.34	33.74
CMC +CAM	226.61	227.92	39.13
MCC+CAM	226.31	228.02	39.08

The DSC curve of lactose shows a endothermic peak corresponding to the dehydration at 148.37 ℃ and the melting point at 218.85℃. The DSC curve of BMs shows three endothermic peak, one corresponding to CAM at 227.42℃, and the others to lactose.

3.2.2 FT-IR results

The FT-IR spectra of CAM and its BM with selected excipients are shown in Fig.6 ~ Fig.10. In the BMs infrared spectrum, the main bands related to CAM were identical to the isolated API spectrum, with some overlapping bands referring to the excipients. In the spectrum of CAM, the characteristic peaks are reported, including the –OH stretching vibration at 3469 cm^{-1} [20]. The peaks between 2980-2750 cm^{-1} are related with alkyl-CH_3 substitution bands, the peak related to carboxyl group in the lactone ring at 1733 cm^{-1} and C=O stretching vibration from ketone group in the lactone ring at 1691 cm^{-1}. In the BM of CAM-MGST, spectrum of the region 1540 cm^{-1} was referred to the excipient, because of the presence of MGST grouping. The same happens with the region of 1604 cm^{-1} that in BMs suffers overlapping.

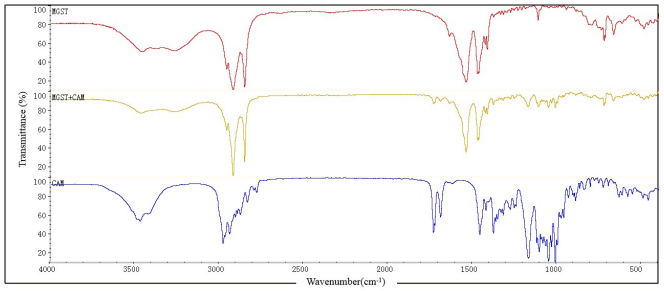

Fig. 6 The FT-IR spectra of BM of CAM - MGST

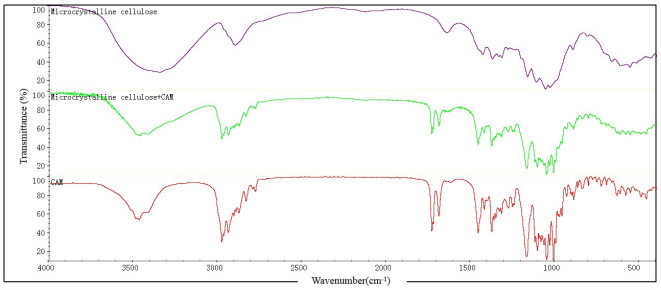

Fig. 7 The FT-IR spectra of BM of CAM – MCC

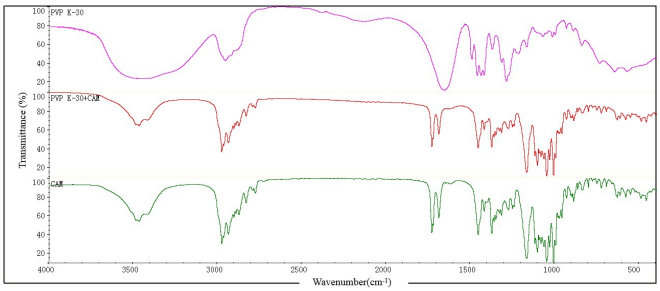

Fig. 8 The FT-IR spectra of BM of CAM - PVP K-30

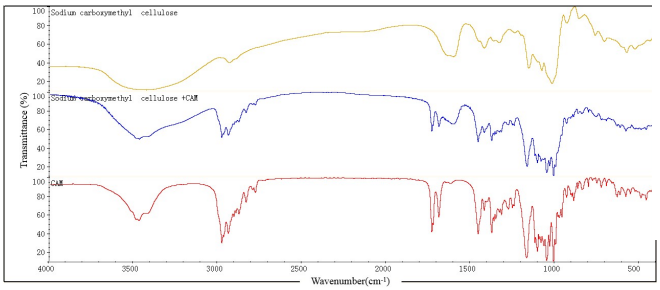

Fig. 9 The FT-IR spectra of BM of CAM - CMC

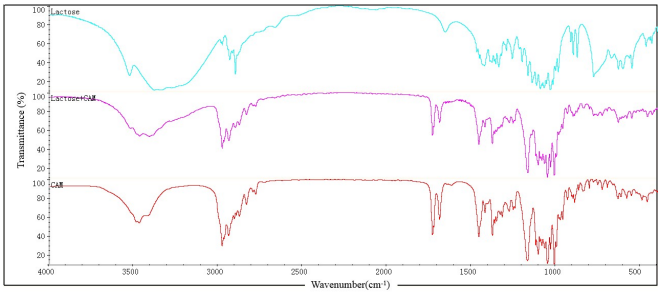

Fig. 10 The FT-IR spectra of BM of CAM - lactose

3.2.3 XRPD results

API, individual excipient and BMs were also characterized by XRPD for quantitative and qualitative assessing any possible crystalline formation of CAM. The XRPD profile of CAM, shown in Fig 11, exhibits a typical polycrystalline diffraction pattern, with a main sharp peak at 8.51° 2θ and secondary peaks at 9.45°, 10.82° and 11.45° 2θ, those characteristic peaks have been reported by Jih-Hua Liu as form II[5]. Based on the results of XRPD, the characteristic peaks of CAM were retained in the BMs, the XRPD patterns of its physical mixtures did not show any new peaks or absence of any parent peaks, which exhibited there was no interaction between API and selected excipients.

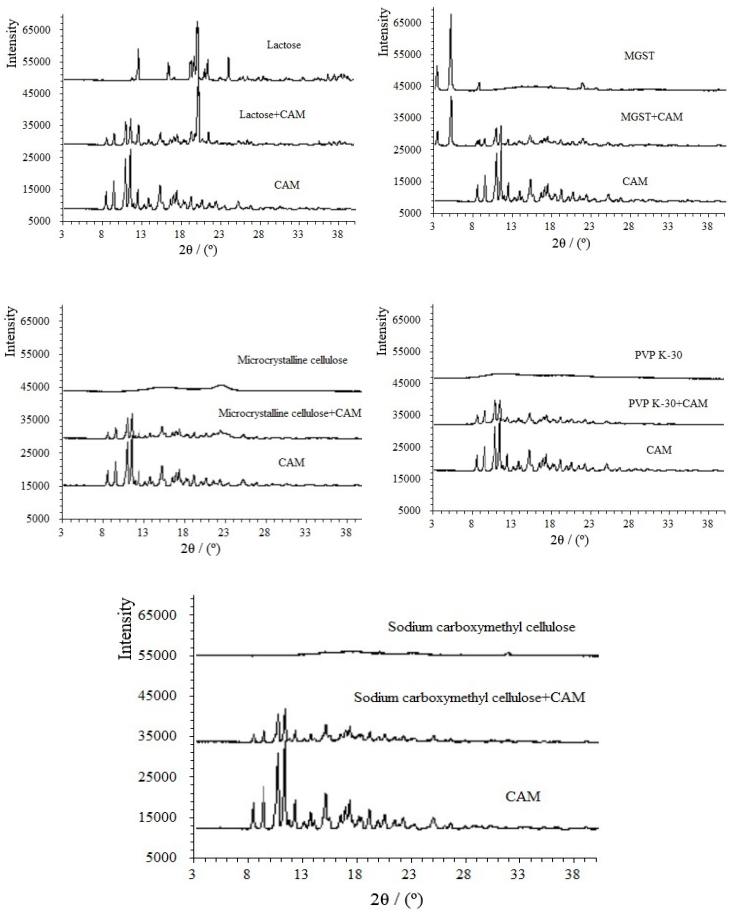

Fig. 11 The XRPD spectra of BMs

3.3 Alcohol prescription simulation

From excipient compatibility experiment, we found that the influence factor of CAM crystal transition maybe another existence. According the preparation process, a series concentration of 50 %, 75 %, 85 %, 95 %, 100 % alcohol 2.5 ml and API about 0.1 g were mixed and stirred 5 min, filter and use resultant decompression drying 30 min in 50 ℃. The powder was determinated by XRPD and DSC analysis, respectively. The characteristics diffraction peaks when alcohol concentration increasing to 85% at 2θ degree were 4.52°, 6.45° and 7.56°. It was consistent with that of form 0 (Fig 12(a)). the DSC results showed that when alcohol concentration increasing to 85%, a wide exothermic peak at 114.95 ℃ was appeared except the sharp endotherm at 226.31 ℃ (Fig 12(b)). The results showed that the crystal form was changed when alcohol concentration increasing to 85%.

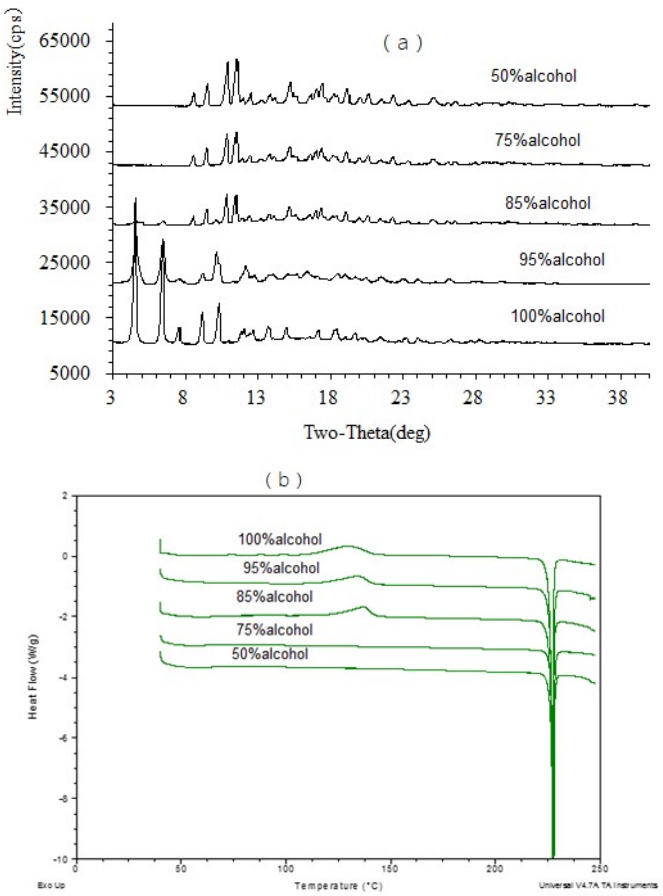

Fig 12. (a)The X-ray diffraction patterns of resultant in the different concentration of alcohol conditions. (b) The DSC curves of resultant in the different concentration of alcohol conditions.

DISCUSSION AND CONCLUSIONS

In our report, the crystal form of API and API in CAM sustained release tablets were confirmed by XRPD. API of the LY and HN pharmaceutical Co., Ltd. shows crystal form Ⅱ. However, the CAM sustained release tablets of LY contains the form Ⅱ, tablets of HN contains the form I and form Ⅱ.

In addition, thermal analysis along with XRPD and FT-IR were also successfully employed to evaluate the compatibility of CAM with selected excipients used in a sustained release tablet formulation. From the mixtures analyzed by DSC, some of the excipients showed different results indicating the existence of possible interaction. Therefore, complementary techniques were selected for further research. Based on the results of FT-IR and XRPD analysis, any pharmaceutical incompatibilities between MGST, lactose and CAM were ruled out. The agreement between the results from each technique demonstrates that DSC was an efficient and rapid method to assess compatibility, the combination of other techniques was an useful method to improve the interpretation of DSC results.

The alcohol prescription simulation results showed that the crystal form in sustained release tablets was changed when alcohol concentration increasing to 85%. The reason of crystal transition that CAM incompatibility with high concentration alcohol as drug adhesive was confirmed.

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REFERENCES

[1] Sherman D, Xiong L, Mankin AS, Melman A. Synthesis and biological investigation of new 4-malonyl tethered derivatives of erythromycin and clarithromycin. Bioorganic & Medicinal Chemistry Letters. 2006, 16:1506-1509.

[2] Inukai K, Takiyama K, Noguchi S, Iwao Y, Itai S. Effect of gel formation on the dissolution behavior of clarithromycin tablets. International Journal of Pharmaceutics. 2017, 521:33-39.

[3] Spanton SG, Henry RF, Riley DA, Liu J-H. Crystal form 0 of clarithromycin. U.S. Patent 5945405. Aug 31, 1999.

[4] Liu J-H, Riley DA, Spanton SG. Crystal form I of clarithromycin. U.S. Patent 5858986. Jan 12, 1999.

[5] Jih-Hua Liu, David A. Rlley. Preparation of crystal form II of clarithromycin. U.S. Patent 5844105. Jul. 29, 1996.

[6] Jih-Hua Liu., Rodger F.Henry., Stephen G. Spanton.. 6-O-methylerythromycin A crystal form III. U.S. Patent 6627743 B1. Dec.3, 1999.

[7] Ilya Avrutov., Lifshitz;l I, Ronen Borochovitz., Basem Masarwa., Edi Schwartz. Processes for preparing clarithromycin polymorphs and novel polymorph IV. U.S. Patent 6599884 B2. Dec 15, 2000.

[8] Gruss. M.. Polymorph of Clarithromycin (Form V). U.S. Patent 20080249035. Oct 9, 2008.

[9] Masood Parvez., M. Saeed Arayne., Rizwana Sabric., Sultana N. Clarithromycin hydrochloride 3.5-hydrate. Acta Crystallo-graphica Section C. 2000,.July, 13;c56:e398-e399.

[10] Iwasaki H, Sugawara Y, Adachi T, Morimoto S, Watanabe Y.. Structure of 6-O-methylerythromycin A (clarithromycin). Acta Crystallographica Section C. 1993, C49:1227-1230.

[11] Tozuka Y, Ito A, Seki H, Oguchi T, Yamamoto K.. Characterization and quantitation of clarithromycin polymorphs by powder X-ray diffractometry and solid-state NMR spectroscopy. Chem Pharm Bull. 2002, 50:1128-1130.

[12] Kimberley Jackson., David Young., Sonia Pant. Drug–excipient interactions and their affect on absorption. PharmSCI Technol Today. 2000, 3:336-345.

[13] Tiţa B, Fuliaş A, Bandur G, Marian E, Tiţa D. Compatibility study between ketoprofen and pharmaceutical excipients used in solid dosage forms. Journal of Pharmaceutical and Biomedical Analysis. 2011, 56:221-227.

[14] Chadha R, Bhandari S. Drug-excipient compatibility screening - role of thermoanalytical and spectroscopic techniques. J Pharm Biomed Anal. 2014, Jan;87:82-97. Epub 2013/07/13.

[15] G. Bruni., L. Amici., V. Berbenni., A. Marini., A. Orlandi. Drug-excipient compatibility studies: Search of interaction indicators. Journal of Thermal Analysis and Calorimetry. 2002, 68:561-573.

[16] A. Marini, V. Berbenni, S. Moioli, G. Bruni, P. Cofrancesco, C. Margheritis, Villa M. Drug excipient compatibility studies by phsico-chemical techniques: The case of indomethacin. Journal of Thermal Analysis and Calorimetry. 2003, 73:529-545.

[17] A. Marini., V. Berbenni., M. Pegoretti., G. Bruni., P. Cofrancesco., C. Sinistri., Villa M. Drug excipient compatibility studies by phsico chemical techniques: The case of atenolo. Journal of Thermal Analysis and Calorimetry. 2003, 73:547-561.

[18] Gao R, Jin Y, Yang Q-Y, Sun B-W, Lin J. Study of stability and drug-excipient compatibility of estradiol and pharmaceutical excipients. Journal of Thermal Analysis and Calorimetry. 2014, 120:839-845.

[19] Ding T, Chen L, Zhai L-H, Fu Y, Sun B-W. Compatibility study of rivaroxaban and its pharmaceutical excipients. Journal of Thermal Analysis and Calorimetry. 2017, 130: 1569-1573.

[20] Manniello MD, Del Gaudio P, Aquino RP, Russo P. Clarithromycin and N-acetylcysteine co-spray-dried powders for pulmonary drug delivery: A focus on drug solubility. Int J Pharm. 2017, 533: 463-469.