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Compatibility Study Of Metformin With Pharmaceutical Excipients

Metformin-Excipient Interaction

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Abstract: Metformin HCl is antihyperglycemic agent used in the treatment of type 2 Non Insulin Dependent Diabetes Mellitus, and pharmaceutical excipients of common use including solvent, binders, diluents and antioxidant, were evaluated for compatibility. A pilot study of MHCl-excipient (antioxidants, binder diluents, disintegrants, glidant, lubricants, pH modifiers, preservatives, solvent, and surfactants, sweetening agents) has been carried out in laboratory. The blends of MHCl with some antioxidants, binder, diluents, disintegrants, glidant, lubricants, pH modifiers, preservatives, solvent developed yellowish coloration and white sticky mass, which intensified with time and also shows changes in UV spectrum. From these data, the blends of excipients polyethylene glycol 6000, polyvinylpyrrolidone, hydroxy propylmethyl cellulose and butylatedhydroxy anisole, with MHCl showed prominent alters were selected for compatibility studies using analytical techniques that relates to the stability of MHCl in dosage form. To confirm the interacting species the drug mixed with each excipient exposed to conditions of 25 ± 3 ^{0}C, 50 ± 2 ^{0}C, 2 - 8 ^{0}C, 40 ± 2 ^{0}C/75 ± 5% RH for 3 months. Differential thermal analysis and Differential scanning calorimetry were used for a screening to find small variations in peak temperatures and/or their associated enthalpy for drug/excipient combinations which indicate some degree of interaction. Additional studies using Fourier transformed infrared spectroscopy confirmed the incompatibility of metformin with above excipients. There was significant change in physical and chemical properties of the blends after 3 months.

Keywords: Metformin, compatibility, excipient, polyethylene glycol 6000, polyvinyl pyrrolidone, hydroxy propylmethyl cellulose, butylatedhydroxy anisole.

Introduction[1-12]

Drugs are rarely administered in pure chemical form and often they are combined with excipients to transfer them into a convenient dosage form. Excipients, although pharmacologically inert can initiate propagate or participate in chemical or physical interaction with quality and performance medication and any impurities present, can stabilize and/or destabilize drug products. The prevention of interaction of drugs with additives or

even packaging devices and stability against microbial action or oxidative degradation demands special attention for ensuring quality of dosage form.

Preformulation is the first step in the rational formulation of an active pharmaceutical ingredient (API). It is a critical phase in drug development where the physicochemical profiling of API and excipient are determined and prototype formulation is made. The performance of solid dosage form is dependent on physicochemical properties of API and the excipients. Concomitant with the choice of excipients is an exhaustive evaluation of drug–excipient interaction and compatibility. The ultimate goal is to identify the critical properties that are considered important in the formulation of stable, effective and safe drug delivery system or dosage form. The evaluation of drug–excipient compatibility is based on inherent properties of the excipient. It is an investigation of the physical-chemical properties of the drug substance, alone and in combination with excipients. Assessment of possible incompatibilities between the drug and different excipients is an important part of preformulation. The formulation of a drug substance frequently involves its blending with different excipients to improve manufacturability and to maximize the product's ability to administer the drug dose effectively.

Selected excipients should play one or more functional role in the final dosage form and therefore it is necessary to understand the function of excipients in the new era of quality by design (QBD) to characterize, understand and control the process as well as product quality. The quality of formulation is defined by stability and study of stability and stability testing techniques is essential for safety of patient, uniform dose of drug throughout the whole of shelf-life of products, legal relevant requirement concern with the identity, strength, purity and quality of drug products[1]. Excipient may also contain impurities[2] or form degradation products which may cause the degradation of drug substance. While physical interaction affects rate of dissolution, uniformity of dose or ease of administration, chemical interaction leads to degradation of active ingredient thus altering the stability and bioavailability behaviour of medication and both type of interaction are considered as incompatibility[3].

The study of drug–excipient compatibility is an important stage in the development of a solid dosage form as their incompatibility can alter the stability and/or the bioavailability of drugs thereby, affecting its safety and/or efficacy. The excipients compatibility studies is used to select the dosage form of component, delineate stability profile of the drug, identify degradation product and understand mechanism of reaction[4]. In pharmaceutical dosage form API are in intimate contact with one or more excipients. Moreover in most of dosage form the quantity of excipients are greater than the amount of API present in dosage form, therefore excipients can have tremendous impact on the performance of API when present in dosage form. It can influence the safety and effectiveness of drug depending upon route of administration. Therefore, understanding of drug-excipients interactions is very important during selection of appropriate excipients for proposed dosage form and for the same there is a need to carry out drug-excipients compatibility studies. Thermal analysis, TGA, DTA and DSC, has been used extensively for chemical stability and compatibility studies[5-9]. HPLC with UV detection is by far the most commonly used method to quantify drug degradation by measuring drug potency, total impurities or the growth of a selected impurity over time and as a function of the storage conditions.

Metformin is hygroscopic in nature and unstable to alkaline pH. Metformin stored at $50 \pm 2\ ^0$C did not show any physical changes and moisture gain while at 2-8 ^{0}C physical changes was observed but slight moisture absorption was calculated. However its storage at 40 ^{0}C/75% RH and $25 \pm 3\ ^0$C demonstrated weight gain and changes in UV and IR absorption spectra. DSC and DTA also signified the degradation of Metformin under these conditions. Based on the observations of physical changes, pH determination, and moisture gain, UV absorption investigated the influence of temperature and humidity on the stability of Metformin alone and in presence of polyethylene glycol 6000, polyvinylpyrrolidone, hydroxy propylmethyl cellulose and butylatedhydroxy anisole, by FTIR, DTA and DSC.

Experimental[1-12]

Material

Metformin HCl (MHCl) was a gift sample from Global Pharma (Mumbai, India). Butylated hydroxyl anisole (BHA) was obtained from Merck (Mumbai, India), polyethylene glycol 6000 (PEG) from Qualigens Fine Chemicals (Mumbai, India). Hydroxy propyl methyl cellulose (HPMC) and polyvinyl pyrrolidone (PVP)

were obtained by Loba Chemei (Mumbai, India), Acetonitrile, Methanol, Triethylamine and all other chemicals used were of analytical grade. The mixed samples consisted of equal weights of MHCl and each excipient was individually weighed into glass ampoule to give composite weights of 40 mg. The physical mixtures was gently prepared at a 1:1 (RNH:excipient) weight ratio by simple mixing with a spatula. The 1:1 w/w ratio was chosen in order to maximize the probability of interaction detection.

Methods

The samples of MHCl and its mixture with different pharmaceutical excipients in 1:1 ratio (20 mg each) stored for 3 months at 50 ± 2^0C in oven, Hicon (New Delhi, India) and 40 ± 2^0C/75 ± 5% RH in stability chamber (Thermolab scientific equipment, Thane, India). The physical changes were recorded visually by comparing the transform in nature, colour, solid characteristic and confirm by using Motic microscope (DMWB1-223 ASC, Canada). pH determination of 0.2% sample solution was carried out by using pH meter (Electronics, India). Solution (8 µg/ml) of MHCl and its blends with excipients was scanned using UV spectrophotometer (JASCO, Tokyo, Japan) in the range of 400-200 nm. Calibration curve was plotted for fresh solution of MHCl; the qualitative estimation was carried out at 232 nm. The fresh and exposed samples were then analyzed using FTIR Spectrophotometer, (Shimadzu-8400S, Kyoto, Japan). Fourty scans were taken in transmission mode with resolution of 4 cm^{-1} in the region of 4000-400 cm^{-1}. Thermal analysis measurements of MHCl as well as blends with excipient were carried out on a differential thermal analysis (DTA) (TA Instruments, USA) and differential scanning calorimeter (DSC) (Perkin Elemer-DSC-7). The samples were scanned in the temperature range of 0-400^{0}C at heating rate of 10^{0}C/min under the flow of nitrogen during the experiment.

Result and Discussion

Preliminary interaction study at 50 ± 2^0C and 40 ± 2^0C/75 ± 5% RH

MHCl and its mixture with different pharmaceutical excipients in 1:1 ratio (20 mg each) stored for 3 months at 50 ± 2^0C and 40 ± 2^0C/75 ± 5% RH were analyzed to determine the possible interaction for physical changes, pH and moisture gain. Qualitative analysis of solutions of MHCl or its mixture with excipient in distilled water equivalent to 8 µg/ml was scanned in the UV region between 200-400 nm. An UV spectrum of MHCl exposed at 50 ± 2^0C and 40 ± 2^0C/75 ± 5% RH and its blends with excipients demonstrated changes in absorbance with time at λmax for MHCl, 232 nm. On the basis of data obtained from preliminary study, PEG, PVP, HPMC and BHA were selected for further investigation of MHCl-excipient interaction and comparatively studied at different storage (25 ± 3^0C, 2 - 8^0C) and accelerated conditions (50 ± 2^0C, 40 ± 2^0C/75 ± 5% RH) for 3 months.

Physical alterations and moisture determination

MHCl was almost stable on storage for 3 months under 50 ± 2^0C and 2 - 8^0C. The weight gain was observed at 40 ± 2^0C/75 ± 5% RH and 25 ± 3^0C which might be associated with moisture absorption. The % Relative humidity (RH) of manufacturing environment has great effect on the moisture level of MHCl as it absorbs maximum amount of moisture at higher % RH. The mixture of MHCl with PEG and PVP stored at 2-8 ^{0}C, 40 ± 2 ^{0}C/ 75 ± 5% RH and 25 ± 3 ^{0}C showed white sticky mass with associated moisture gain was observed. However at 50 ± 2 ^{0}C did not demonstrate any moisture gain as well no degradative events were determined from the mixture. The blends of MHCl with HPMC and BHA showed significant moisture gain at all storage conditions shown in table 1.

pH Determination

As shown in table 1, MHCl and its blends with PEG, PVP, HPMC and BHA exhibited pH 6-7 throughout the period of investigation.

UV Spectrophotometric determination

The spectral changes in the solutions of MHCl in methanol equivalent to 8 µg/ml were scanned in the UV region between 200-400 nm. The absorbance of exposed MHCl increased as compared to MHCl. From the above result it can be concluded that the MHCl is temperature sensitive.

Table 1: Physical change, pH and moisture determination of MHCL and its blends with excipients

Sample	Conditions	Physical Changes	pH	% Weight change
MHCL	I	Dark yellow	6.8	-19.05
	II	Brown wet mass	7.05	8.05
	III	Yellow wet mass	6.96	2.38
	IV	Black brown liquid	6.97	55.81
MHCL-PEG	I	Dark Brown wet mass	6.62	-17.44
	II	Dark Brown wet mass	6.93	9.64
	III	Yellow brown wet mass	6.88	7.06
	IV	Black brown liquid	7.01	44.30
MHCL-PVP	I	No Change	6.52	-26.19
	II	No Change	6.83	16.67
	III	No Change	6.83	3.70
	IV	Dark brown wet mass	6.98	60.24
MHCL-HPMC	I	No Change	6.61	-21.52
	II	No change	6.97	3.70
	III	No change	6.9	9.20
	IV	Dark brown wet mass	6.86	71.08
MHCL-BHA	I	No Change	6.95	-14.81
	II	No Change	7.2	5.88
	III	No Change	7.4	4.88
	IV	Brown wet mass	7.04	68.35

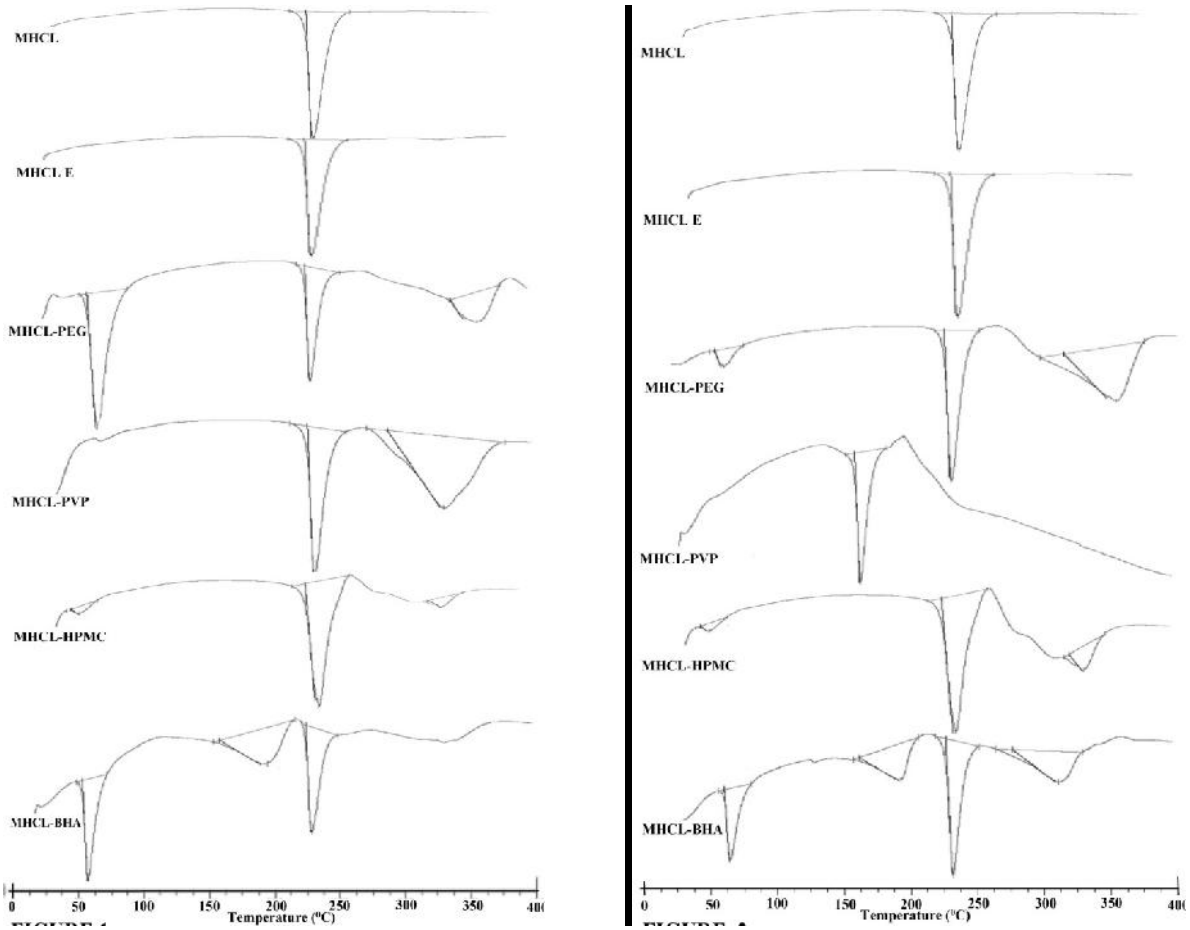
Conditions

I 50 ± 2^0C III $2 - 8^0$C

II 25 ± 3^0C IV 40 ± 2^0C/$75 \pm 5\%$ RH

Thermal Analysis

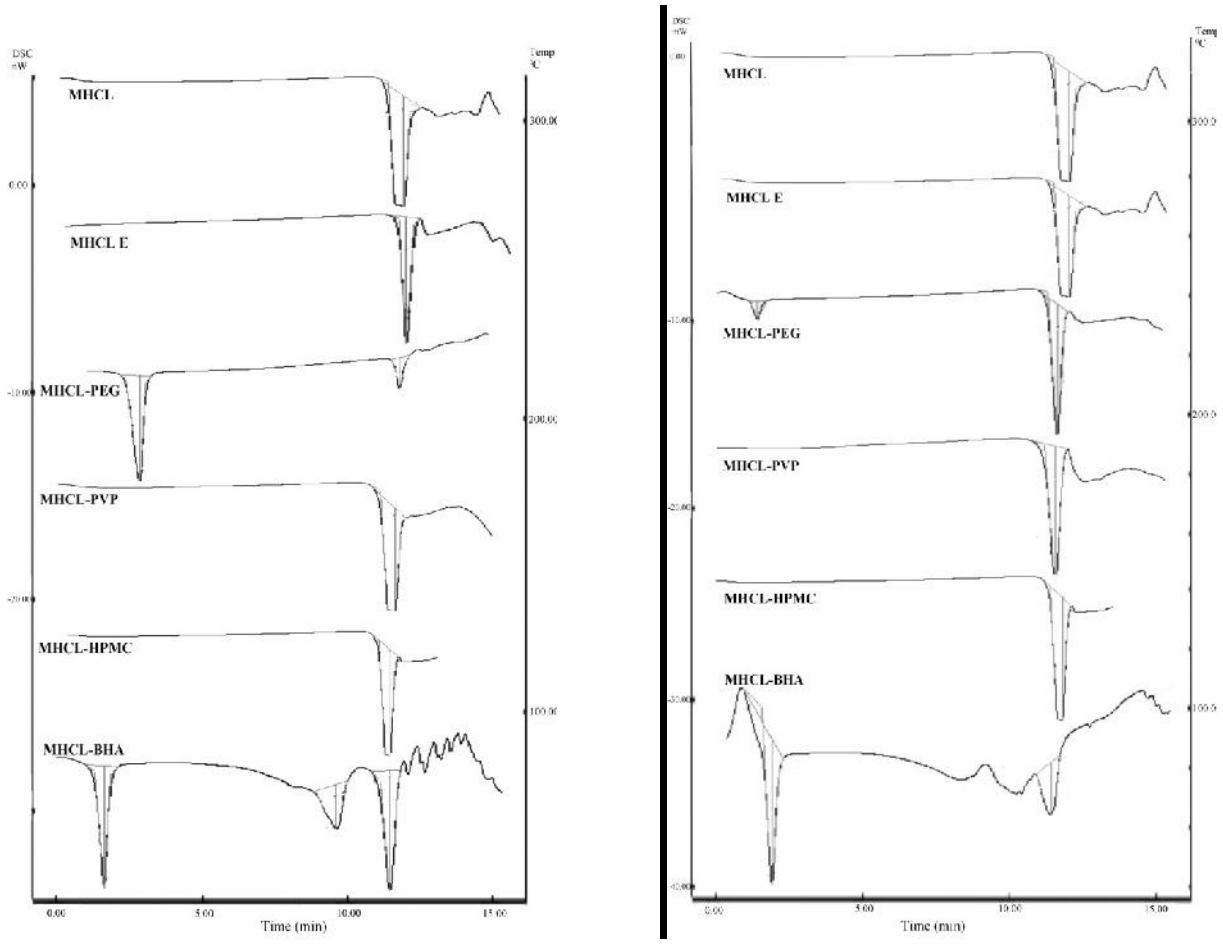
DTA thermogram of exposed MHCl showed one sharp endothermic peak one at 230.66 ^{0}C (onset at 225.26 ^{0}C) corresponding melting of MHCl and DSC thermogram exhibited one sharp endothermic peak at 239.98 ^{0}C (onset at 232.38 ^{0}C and end at 245.93 ^{0}C) corresponding melting point of MHCl as shown in Figs. 1(A) and 2(A), respectively. The DTA and DSC thermogram of MHCl stored at mentioned conditions exhibited all endo/exothermic peak as present in MHCl predicted thermal stability.



(A) **(B)**

Figure 1: Overlain of DTA thermogram of MHCL and MHCL/alone or its blends with PEG, PVP, HPMC and BHA stored at (A) 25 ± 3 ^{0}C and (B) 40 ± 2^{0}C/75 ± 5% RH for 3 months.

Thermal behavior of MHCl-PEG stored at 25 ± 3 ^{0}C for 3 months by DTA was shown in Figure 1(A), exhibited one sharp endothermic peak at 229.48 ^{0}C (onset at 225.44 ^{0}C) corresponding melting of MHCl, and one endothermic peak at 68.82 ^{0}C (onset at 59.67 ^{0}C) corresponding melting of PEG and one additional broader peak at 356.92 ^{0}C corresponding to formation of new compound. Thus the blend exhibited thermal characteristics of individual components of blend. Hence interaction can be said to occur in exposed blends. DSC thermogram of MHCl-PEG stored at 25 ± 3 ^{0}C was shown in Figure 2(A), exihibited sharp endothermic peak at 236.48 ^{0}C (onset at 232.78 ^{0}C and end at 242.05 ^{0}C) corresponding melting of MHCl and endothermic peak at 66.90 ^{0}C (onset at 61.08 ^{0}C and end at 72.53 ^{0}C) corresponding melting of PEG. Thus the blend exhibited thermal characteristics of individual components of blend. DTA thermogram of exposed MHCl-PEG, one sharp endothermic peak at 230.53 ^{0}C (onset at 225.39 ^{0}C) corresponding to melting of MHCl and two broad peak, one at 64.56 ^{0}C (onset at 57.79 ^{0}C) and 350.64 ^{0}C (onset at 312.32 ^{0}C) was observed corresponding to thermal decomposition of more than one component of MHCl storage for 3 months at 40 ± 2 ^{0}C /75 ± 5 % RH shown in Figure 1(B). Thermal behaviour of MHCl-PEG stored at 40 ± 2 ^{0}C/75 ± 5% RH by DSC was different from MHCl as shown in Figure 2(B). As depicted from the thermogram of MHCl, endothermic peak at 235.42 ^{0}C (onset at 231.51 ^{0}C and end at 241.96 ^{0}C) corresponding to melting of MHCl was observed. However in exposed MHCl-PEG two endothermic peak one at 235.42 ^{0}C (onset at 231.42 ^{0}C and end at 241.96 ^{0}C) and other sharp endothermic peak at 62.01 ^{0}C were observed, corresponding melting of MHCl with endothermic decomposition.



(A) **(B)**

Figure 2: Overlain of DSC thermogram of MHCL and MHCL/alone or its blends with PEG, PVP, HPMC and BHA stored at (A) 25 ± 3 ^{0}C and (B) 40 ± 2^{0}C/75 ± 5% RH for 3 months.

DTA thermogram of MHCl-PVP stored at 25± 3 ^{0}C for 3 months was different from MHCl as shown in Figure 1(A). As depicted from the thermogram of exposed MHCl-PVP, one sharp endothermic peak at 229.66 ^{0}C (onset at 224.02 ^{0}C) corresponding melting of MHCl and one broad peak at 328.09 ^{0}C (onset at 284.88 ^{0}C) was observed corresponding to thermal changes occurred in composition of MHCl-PVP and its DSC thermogram exihibited one broad endothermic peak at 238.48 ^{0}C (onset at 231.37 ^{0} C) shown in Figure 2(A). Thermal behaviour of MHCl-PVP stored at 40 ± 2 ^{0}C/75 ± 5 % RH by DTA was different from MHCl as shown in Figure 1(B)**.** As depicted from the thermogram of exposed MHCl-PVP, one sharp endothermic peak at 227.82 ^{0}C (onset at 220.75 ^{0}C) corresponding melting of MHCl and one broad peak at 362.06 ^{0}C (onset at 323.06 ^{0}C) was observed corresponding to thermal changes occurred in composition of MHCl storage for 3 months at 40 ± 2 ^{0}C/75 ± 5 % RH. Thermal behaviour of MHCl-PVP stored at 40 ± 2 ^{0}C/75 ± 5 % RH for 3 months by DSC was different from MHCl as shown in Figure 2(B). As depicted from the thermogram of exposed MHCl-PVP, endothermic peak at 233.13 ^{0}C (onset at 228.22 ^{0}C and end at 239.97 ^{0}C) corresponding to melting of MHCl was observed with endothermic decomposition (shifting of peak MHCl).

DTA thermogram of MHCl-HPMC stored at 25 ± 3 ^{0}C for 3 months, was almost same as MHCL as shown in Figure 1(A). As depicted from the thermogram of exposed MHCl-HPMC one sharp endothermic peak at 236.39 ^{0}C (onset at 225.67^{0}C) corresponding melting of MHCl indicates no prominent changes. Thermal behaviour of MHCl-HPMC stored at 25± 3 ^{0}C for 3 months by DSC was different MHCL as shown in Figure 2(A). As depicted from the thermogram of exposed MHCl-HPMC one broad endothermic peak at 237.31 ^{0}C (onset at 234.32 ^{0}C and end at 244.91 ^{0}C) corresponding melting of MHCl with endothermic decomposition. Thermal behaviour of MHCl-HPMC stored at 40 ± 2 ^{0}C /75 ± 5 % RH for 3 months by DTA was different from MHCL as shown in Figure 1(B). As depicted from the thermogram of exposed MHCl-HPMC one sharp endothermic peak at 235.38 ^{0}C (onset at 224.61^{0}C) and two broad endothermic peak one at 330.65 ^{0}C (onset at

319.34 ^{0}C) and other at 52.27 ^{0}C (onset at 45.39 ^{0}C) corresponding melting of MHCl with decomposition with formation of new impurity, when compared the MHCl. Thermal behaviour of MHCl-HPMC stored at 40 ± 2 ^{0}C/75 ± 5 % RH for 3 months by DSC was different MHCL as shown in Figure 2(B). As depicted from the thermogram of exposed MHCl-HPMC one broad endothermic peak at 238.32 ^{0}C (onset at 233.22 ^{0}C and end at 243.93 ^{0}C) corresponding melting of MHCl with endothermic decomposition.

DTA thermogram of MHCl-BHA exposed to 25 ± 3 ^{0}C showed a sharp endothermic peak of BHA and MHCl at 63.65 ^{0}C and 230.43 ^{0}C respectively. Additionally, broader endothermic peak at 196.99 ^{0}C might be due to formation of new compound as a result of interaction. DSC thermogram of MHCl-BHA exposed to 25 ± 3 ^{0}C showed a sharp melting endotherm of BHA and MHCl at 64.18 ^{0}C and 232.52 ^{0}C respectively with an additional broad endotherm at 200.59 ^{0}C indicating decomposition with formation of new compound shown in Figure 1(A) and 2(A), respectively. Thermal behaviour of MHCl-BHA stored at 40 ± 2 ^{0}C/75 ± 5 % RH for 3 months by DTA was different from unexposed sample as shown in Figure 1(B). As depicted from the thermogram of unexposed MHCl-BHA, sharp endothermic peak at 229.51 ^{0}C (onset at 224.16 ^{0}C and end at 149.37 ^{0}C) corresponding to melting of MHCl was observed. Two broad endoderm at 159.29 ^{0}C and 308.37 ^{0}C and also one sharp endoderm at 63.27^{0}C were observed corresponding to thermal decomposition of more than one component. Thermal behaviour of MHCl-BHA stored at 40 ± 2 ^{0}C/75 ± 5 % RH for 3 months by DSC was different from MHCL as shown in Figure 2(B). As depicted from the thermogram of exposed MHCl-BHA one broad endothermic peak at 227.66 ^{0}C (onset at 219.22 ^{0}C and end at 233.43 ^{0}C) and other peak at 63.76 ^{0}C (onset at 59.43 ^{0}Cand end at 219.22 ^{0}C) corresponding melting of MHCl with a decomposition. In all, this comparison indicated storage for 3 months at 40 ± 2 ^{0}C/75 ± 5% RH degrades MHCl with BHA into at least 4 different degradation products. DSC thermogram of blends stored at 40 ± 2 ^{0}C/75 ± 5% RH showed sharp endothermic peak at 227.60 ^{0}C of melting of MHCl and 63.70 ^{0}C for BHA melting with a broad exotherm around 200 ^{0}C corresponding melting of MHCl with formation of new compound.

FTIR Analysis

FTIR spectrum of MHCl exhibited entire characteristic peak N-H stretching, C=N stretching, C-N stretching, C-H bending at 3397.96 cm^{-1}, 1629.48 cm^{-1}, 1061.62 cm^{-1}, 1475.28 cm^{-1} respectively when compared with reported reference spectra of MHCl. MHCl stored at 50 ± 2 ^{0}C exhibited all peaks as compared with MHCl indicate no chemical changes. The bands are broaden as well as peak for functional group shifted slightly when exposed to 2-8 ^{0}C, 25 ± 3 ^{0}C and 40 ± 2 ^{0}C/ 75 ± 5 % RH which may be associated with higher humidity condition, suggests slight changes in MHCl on exposure conditions at 40 ± 2 ^{0}C/75 ± 5 % RH.

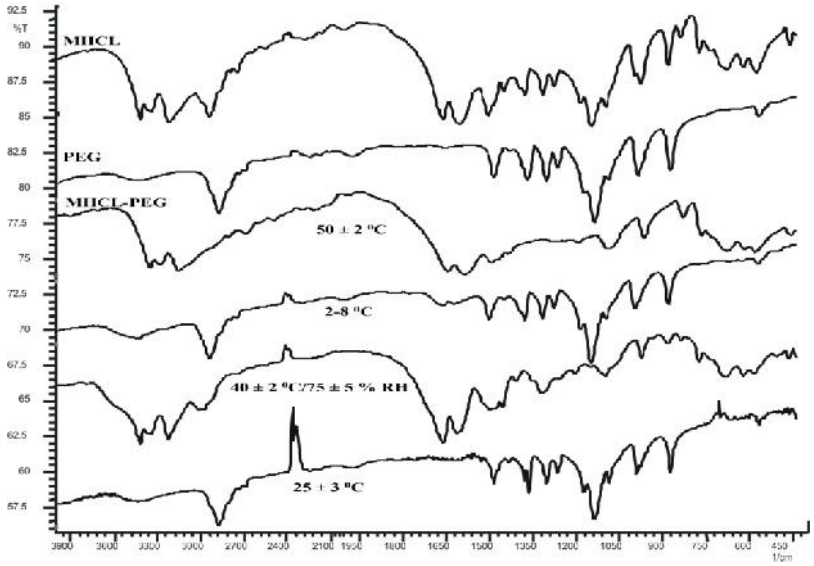


Figure 3: Overlain of FTIR spectrum of MHCL, PEG and MHCL blend with PEG stored at 50 ± 2^{0}C, 2 - 8^{0}C, 40 ± 2^{0}C/75 ± 5% RH and 25 ± 3^{0}C for 3 months

FTIR spectrum of exposed MHCl-PEG at 25 ± 3 ^{0}C in Figure 3, showed disappearance of peak at 3397.13 cm^{-1}and 3310.12 cm^{-1} corresponding to N-H stretch and addition of 1359.72 cm^{-1} corresponding C-H bending, when compared with the FTIR spectra of MHCl. Peak at 1629.72 cm^{-1}of C=N stretch peak was significantly reduced in intensity, but appeared at the same frequency which indicated chemical changes due to prominent interaction between MHCl and PEG. The disappearance of -NH- peak of MHCl could be due to hydrogen bonding between the hydrogen atom at -NH- of MHCl and one of the ion pair of oxygen atom in PEG, whereas at 2-8 ^{0}C showed disappearance of peak at 3298.05 cm^{-1} (C-H stretch) and 1359.72 cm^{-1} corresponding (C-H bending), 3371 cm $^{-1}$ corresponding to -NH- stretch indicate chemical changes in the blend MHCl-PEG due the hydrogen bonding. Earlier reports suggested the similar type of interaction identified by changes in the IR profile of the solid dispersion of glicazide [10].

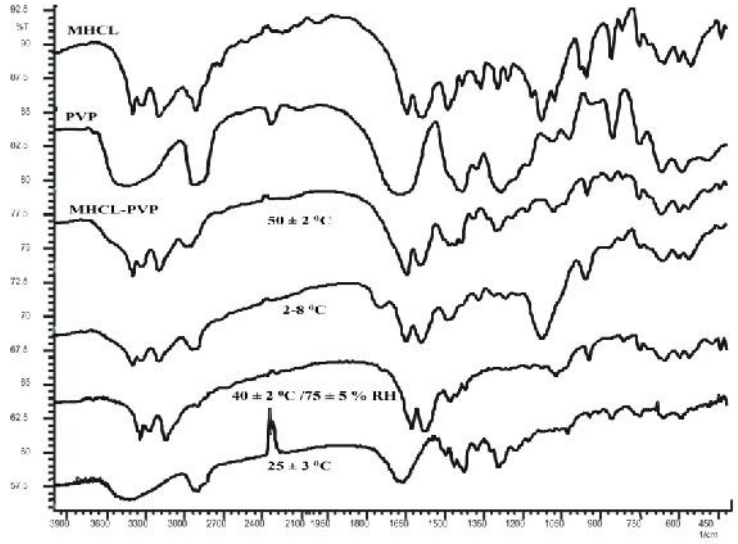


Figure 4: Overlain of FTIR spectrum of MHCL, PVP and MHCL blend with PVP stored at 50 ± 2^{0}C, 2 - 8^{0}C, 40 ± 2^{0}C/75 ± 5% RH and 25 ± 3^{0}C for 3 months

The FTIR analysis of exposed MHCl-PVP at 2-8 ^{0}C showed disappearance of C-N stretching peaks at 1060.78 cm^{-1}. This could be due to hydrogen bonding between the hydrogen at -NH- of MHCl and carbonyl group in PVP. Whereas, FTIR of the blends stored at 40 ± 2 ^{0}C / 75 ± 5 % RH was with the absence of C-H bend peak at 958.56 cm^{-1} and 696.25 cm^{-1} indicating chemical interaction involving hydrogen bonding whereas similar blends stored at 25 ± 3^{0}C showed disappearance of peaks at 3298.53 cm^{-1} of C-H stretch, 3310.21 cm^{-1} of N-H stretch indicating the involvement of -NH- group in hydrogen bonding with -C=O of PVP as shown in Figure4. Additionally as reported earlier broadening and the shifting of the absorption bands of the functional group of the drug was depicted from the IR spectra[11].

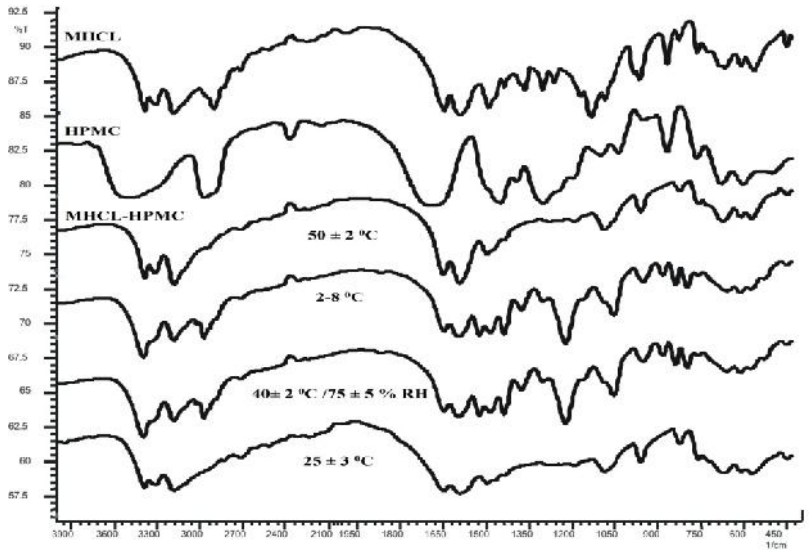


Figure 5: Overlain of FTIR spectrum of MHCL, HPMC and MHCL blend with HPMC stored at 50 ± 2^{0}C, 2 - 8^{0}C, 40 ± 2^{0}C/75 ± 5% RH and 25 ± 3^{0}C for 3 months

As shown in Figure 5, FTIR spectrum of MHCl-HPMC blends stored at 50 ± 2 ^{0}C 40 ± 2 ^{0}C/75 ± 5 % and 2-8^{0}C showed disappearance of the peaks at 842 cm^{-1} of C-H bending and 1110.12 cm^{-1} of C-N stretching whereas the peak of C=N stretch at 1240.12 cm^{-1} was shifted to 1204 cm^{-1}. However, peak at 958.12 cm^{-1} of C-H bending was substituted by C-H bend at 1039 cm^{-1} while peak 1284.32 cm^{-1} was with reduced intensity in MHCl-HPMC blends stored at 25 ± 3 ^{0}C. It seems that intermolecular hydrogen bonding may be associated with observed changes in the blends.

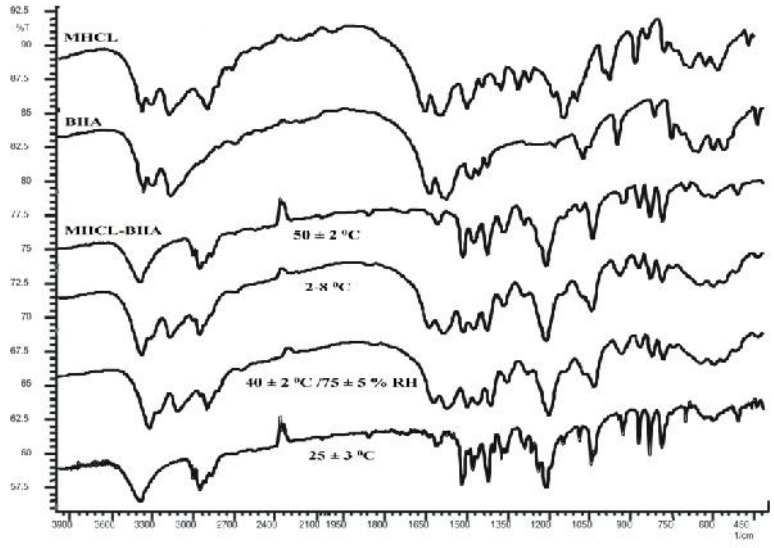


Figure 6: Overlain of FTIR spectrum of MHCL, BHA and RNH blend with BHA stored at 50 ± 2^{0}C, 2 - 8^{0}C, 40 ± 2^{0}C/75 ± 5% RH and 25 ± 3^{0}C for 3 months

FTIR spectrum of MHCl-BHA exposed to 50 ± 2 ^{0}C shown in Figure 6 demonstraed absence of peaks at 885 cm$^{-1,}$ 958.56 cm^{-1} and 1348.11 cm^{-1} corresponding C-H bending. Peak at 1441.53 cm^{-1} corresponding to C-H bending, disappeared from the exposed MHCl-BHA at 2-8 ^{0}C and 40 ± 2 ^{0}C /75 ± 5% RH when compared with the FTIR spectra of MHCl. However, additional peak at 717.12 cm^{-1}corresponding C-H stretch observed at

$25 \pm 3\ ^0C$, indicating the observed chemical changes in the blend MHCl-BHA may be due to hydrogen bonding or phenoxyl free radical formed by BHA [12].

Conclusion

The above investigation suggest that all the excipients studied here are resulting into the physical interaction with as evident from the physical changes, determination of moisture absorption, DSC, DTA, UV determination and FTIR analysis. MHCl and its blend with PVP, BHA stored at $25 \pm 3\ ^0C$ and $40 \pm 2\ ^0C/75 \pm 5$ % RH demonstrated the prominent interactions. The chemical incompatibilities demonstrated by FTIR and DSC/DTA studies seems to be involved hydrogen bonding and oxidation by radical species however in some cases interaction was limited only to physical and no chemical incompatibility was determined.

Conflict of Interest

Authors report no conflict of interest.

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