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RESEARCH ARTICLE

COMPATIBILITY SCREENING OF VIDAGLIPTIN WITH IONIC AND NON-IONIC POLYMERIC EXCIPIENTS FOR THE DESIGN OF EXTENDED RELEASE DELIVERY SYSTEM

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Abstract

Studies of drug-polymer compatibility play an important role in the preformulation stage for the development of pharmaceutical dosage forms. The potential physical and chemical interactions between drugs and polymer can affect the chemical nature, stability and bioavailability of the dosage form and as a result in the therapeutic response in the clinical phase. The present study reveals the thermal and spectroscopic study of physical mixtures of Vildagliptin (VDG) and HPMC in combination with cationic polymers chitosan, anionic polymers NaCMC and nonionic polymers PEO for extended release (ER). In the first phase of the study, differential scanning calorimeter (DSC) was used as tool to detect any interaction. In the next phase, a Fourier Transform Infrared Spectroscopy (FT-IR) technique was used to confirm and to investigate the type of the possible interactions between the components. In both cases, the spectroscopic data revealed that the analysed polymeric excipients did not show any affect on the VDG. Results of the present study indicated the suitability of the HPMC K4M hydrophilic matrix polymers in combination with cationic polymers, anionic polymers and non-ionic polymers in the preparation of extended release formulation of VDG.

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Introduction:-

A complete characterization and understanding of physicochemical interactions of an active pharmaceutical ingredient (API) in the dosage forms is an integral part of preformulation stage of new dosage form development as it is most desirable for consistent efficacy, safety and stability of a drug product. In a dosage form, an API comes in direct contact with other components (polymers and other excipients) of the formulation that facilitate the administration and release of an active component. They can also stabilize it against degradation from the environment. Although excipients are pharmacologically inert, they can interact with drugs in the dosage form. The physical and chemical interactions between the drugs and polymeric excipients can affect the chemical nature, the stability and the bioavailability of the drug products, and consequently, their therapeutic efficacy, safety. Careful selection of the polymeric excipients are required for a robust and effective formulation of dosage forms that make administration easier, improve patient compliance, promote release and bioavailability of the drug and increase its shelf life. Thus, compatibility screening of an API with polymeric excipients or other active ingredients is

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recognized as one of the mandatory factors and is at the fore front of drug product science and technology research (Chadha and Bhandari, 2014; Rus et al., 2012). The active substance/polymeric excipient compatibility studies play the role of identifying in an as short as possible time interactions between potential polymeric excipients and the active substance (Bharate et al., 2010; Giron 1998; Sims et al. 2003).

The most frequently methods for the physical-chemical investigation with the view of detecting the possible interactions between the polymeric excipients and the active drug substance are thermal analysis (DSC, DTA, DTG, ITC), spectroscopic methods (FT-IR, X-ray diffraction, NMR), chromatographic methods (LC, LC-MS/MS), the dissolution tests etc. (Elkordy and Essa, 2010; Guo et al., 2006; Newa et al., 2007; Budura et al. 2011). The most sensitive methods for detection of the possible interaction are the thermal analytic ones, but they can be unspecific and the result is difficult to interpret and they can very frequently indicate false positive or false negative results.

Differential scanning colorimetry (DSC) is currently the leading technique in this field [3]. The main benefit of DSC, rather than stressed storage methods, is its ability to quickly screen the potential excipients for incompatibilities derived from the appearance, shifts or disappearance of peaks and/or variations in the corresponding ΔH, enthalpy of transition (Defang et al., 2005). Other features such as low sample consumption also make it an attractive method. Although DSC is unquestionably a valuable technique, interpretation of the data may not be straightforward. In this method, the sample is exposed to high temperatures (up to 300°C or more), which in reality is not experienced by the dosage form. Thus, DSC results should be interpreted carefully, as the conclusions based on DSC results alone can be often misleading and inconclusive (Thumma and Repka, 2009).

The IR spectroscopic methods are less sensitive from this point of view, but they are complementary for the thermal-analytical techniques, especially due to the detection of the atom groups involved in the excipient/API interaction and they allow the quantitative estimation of these interactions (Elkordy and Essa, 2010; Newa et al., 2007; Oberoi et al., 2005).

The aim of the study was to investigate the compatibility of HPMCK4M polymer with excipients of ionic and non-ionic nature as release retardant polymer for the design of extended release delivery systems using highly water soluble oral anti-diabetic drug.

Material and Methods:-

Materials:

The VDG was obtained from Sigma Aldrich, Bangalore. Polymeric Excipients tested were procured from certified vendors such as HPMC K4M (Lobachemie), Chitosan 220 from CIFT Cochin; Sodium CMC was obtained from National chemicals, Baroda; Poly (ethylene oxide) (Polyox WSR 303, PEO) from The DOW Chemical Company were purchased in Mumbai, India

Samples preparation

For DSC analysis, three prototype formulas of polymeric excipients, consisting of physical mixtures of Chitosan: HPMC K4M (Formula 1), NaCMC: HPMC K4M (Formula 2), PEO 1105: HPMC K4M (Formula 3) respectively. The ratio between the components was kept at 1:1. Mixtures of these excipients with the active drug substance (VDG) were prepared in a ratio of 1:1, 1 2 and 1:3.

For the FT-IR analysis physical mixtures of the above combinations were prepared in a ratio of 1:1. They are mixed in a mortar to obtain a physical mixture that was sieved through 120 µm sieve. All the samples were kept for a week at room-temperature for further analysis.

Appropriate quantities of the drug and polymers were weighed in different ratios as mentioned in table. The weighed drug and the polymers will be blended physically and will be transferred to glass vials and sealed. The sealed vials are placed inside stability chamber at 25 ◦C/60% RH, 40 ◦C/75% RH for a period of 4 weeks and samples are analyzed for any significant change.

Differential scanning calorimetry study

A Mettler Toledo DSC thermal analysis system (Mettler Inc., Schwerzenbach, Switzerland) was used for thermal analysis of the drug-polymer mixtures. Approximately 2-5 mg of VDG and Polymeric excipients or their binary mixtures were examined in the temperature range between 40 ◦C and 300 ◦C, in a normal covered aluminium pan

(three pin holes were applied in the cover). The heating rate was 10 °C min^{-1}. Nitrogen was used as carrier gas at a flow rate of 10 Lh-1 during the DSC investigation (Thumma and Repka, 2009; Kiss et al., 2006).

Fourier transform infrared spectroscopy study

FT-IR spectra of the VDG, binary polymeric mixtures and each binary mixture with the active substance were recorded in the scanning interval of 400–4000 cm^{-1} and optical resolution was set at 4 cm^{-1} using a Schimadzu FT-IR instrument (Japan). Standard KBr pellets were prepared from analytical grade KBr using 0.5 mg of VDG or 1.0 mg of binary mixture. The spectra were recorded with the use of software, and all spectral interpretations were done (Thumma and Repka, 2009; Defang et al., 2005).

Isothermal Stress Testing (IST)

The samples of pure drug and homogeneous mixture of drug with each excipient were kept at accelerated conditions of 35 °C and 45 °C in sealed glass vials (Kandarpa et al., 2012; Jinnawar and Gupta, 2012). After mixing on a vortex mixer for 2 min, water (10.0% w/w) was added in each of the vials, and the drug-excipient blends were further mixed with a glass capillary tube (both the ends of which was heat sealed). To prevent the loss of material, the capillary was broken and left inside the vial. Each vial was sealed using a Teflon-lined screw cap and stored at 35 °C and 45 °C in a hot air oven (Universal, Narang Scientific, New Delhi, India). Drug-excipient blends without water stored in a refrigerator served as controls. The drug-excipient blends were periodically examined for any unusual color change. The samples were quantitatively analyzed in a UV-visible spectrophotometer (Shimadzu, Tokyo, Japan) at 244 nm after 3 weeks of storage at the above conditions. For sample preparation, 2.0 mL of methanol was added to each vial to solubilize the drug. The mixture was vortexed for 3 min and transferred to a 100 mL volumetric flask. Vials were rinsed twice with 2.0 mL of methanol and transferred to the volumetric flask, and the volume was made up to 100 mL with phosphate buffer pH 7.4. The samples were filtered through 0.45 micron nylon membrane filters. After appropriate dilutions, each filtrate was analyzed in a UV-visible spectrophotometer at 244 nm, and the drug content was determined from the calibration curve prepared within the expected range.

Results And Discussion:-

Drug-polymer compatibility testing by DSC

The changes, if any, in the thermal characteristics of VDG in the prototype polymeric excipient mixtures formulas were studied using a differential scanning calorimeter. The DSC thermogram of VDG (Figure 1) shows a sharp endotherm at 158.58 °C with the heat of fusion was found to be 489.19 J/g. The melting peak of VDG in polymeric excipient mixtures HPMC+Chitosan, HPMC+NaCMC and HPMC+PEO found to be 154.18, 153.97 and 152.82 respectively. The melting point of VDG found to be small and decreased in intensity in drug- polymer mixtures. The thermo-analytical data of DSC of VDG and drug-polymeric excipient mixtures were presented in Table 1.

Table 1:- Thermoanalytical data of VDG and polymers.

Drug+Polymers	Tpeak (fusion)/oC	ΔH (fusion)/J g-1
VDG	158.58	489.19
HPMC+Chitosan	105.33	1259.14
HPMC+NaCMC	109.31	1056.85
HPMC+PEO	65.00	321.04
VDG+ HPMC+Chitosan	154.18	166.63
VDG+ HPMC+NaCMC	153.97	149.69
VDG + HPMC+PEO	152.82	100.73

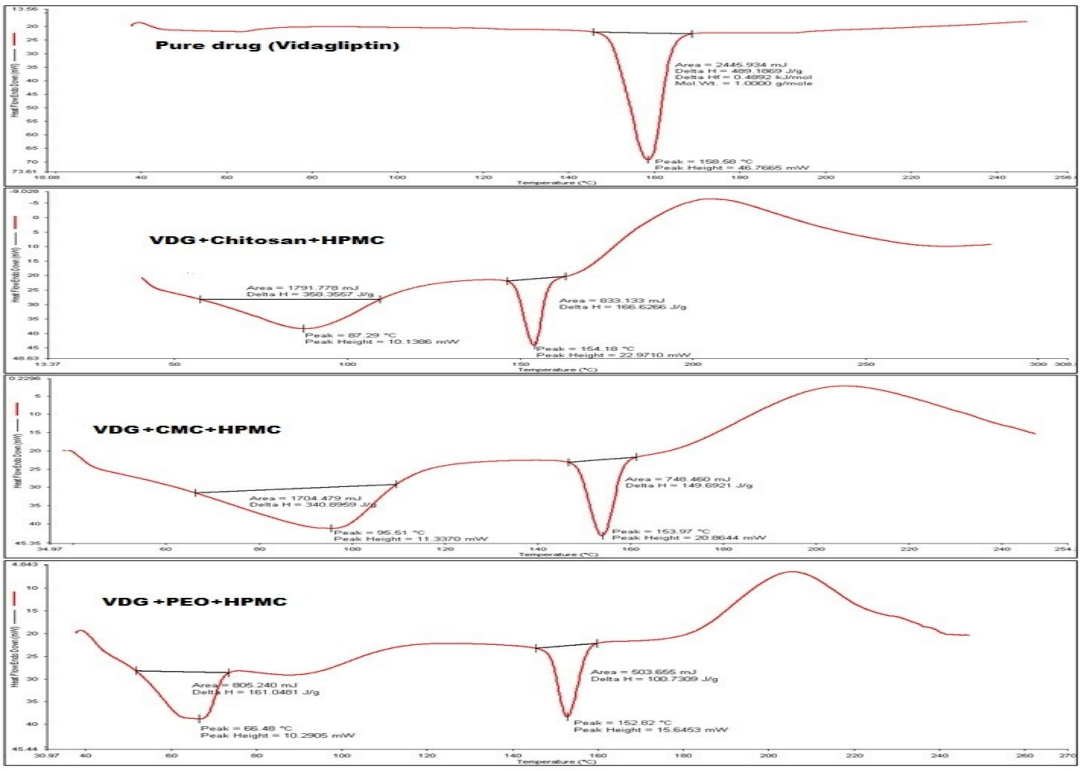

Figure 1:- Comparative DSC studies of 1:1 binary mixtures of drug with cationic, anionic and non-ionic polymers.

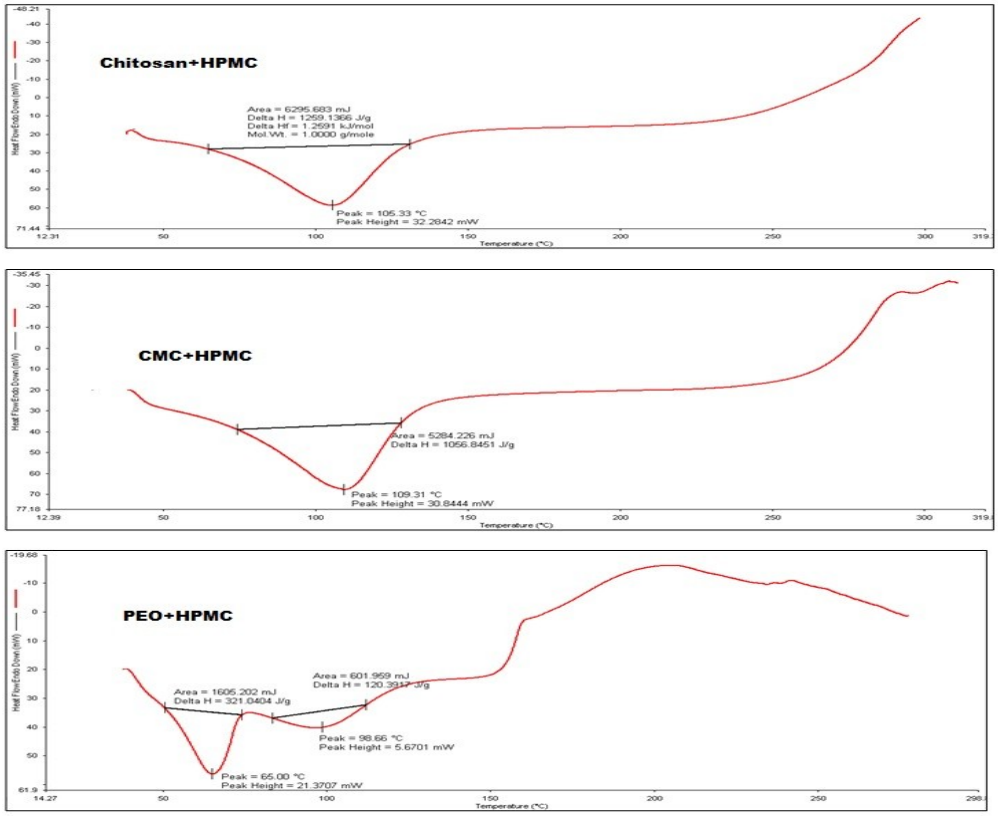

Figure 2:- Comparative DSC studies of 1:1 binary mixtures of cationic, anionic and non-ionic polymers without drug.

Drug–polymer interaction studies by FT-IR

FT-IR studies are performed to confirm the possible interactions between API and the various ionic and non-ionic polymers to reveal their nature before included in the prototype extended release formulations. The FT-IR spectra of VDG shows two characteristic strong absorption bands at 2910.73 cm^{-1} (C-H stretching vibration of alkane), 1653.46 cm^{-1} (stretching vibration C=O) and 1401.56 cm^{-1} (C-H bending vibration of alkane).

In order to detect the possible spectral changes due to the polymers/API interactions, the various spectral bands were analyzed and compared with that of standard VDG (Figure 3).

The IR spectra of physical mixture of VDG with each polymeric mixture (HPMC+Chitosan, HPMC+NaCMC and HPMC+PEO) showed respective identical peaks of drug without any significant shifts in their band range or a small shift but within the allowable range. This revealed the presence of no interaction with the drug proving its compatibility. There was no appearance of new bands in IR spectra confirming that it did not show change in structural functional groups of drugs. FT-IR spectral analysis confirms that there is no appearance or disappearance of any characteristic peaks of pure drug VDG in the physical mixture of all extended release polymers (Figure 3).

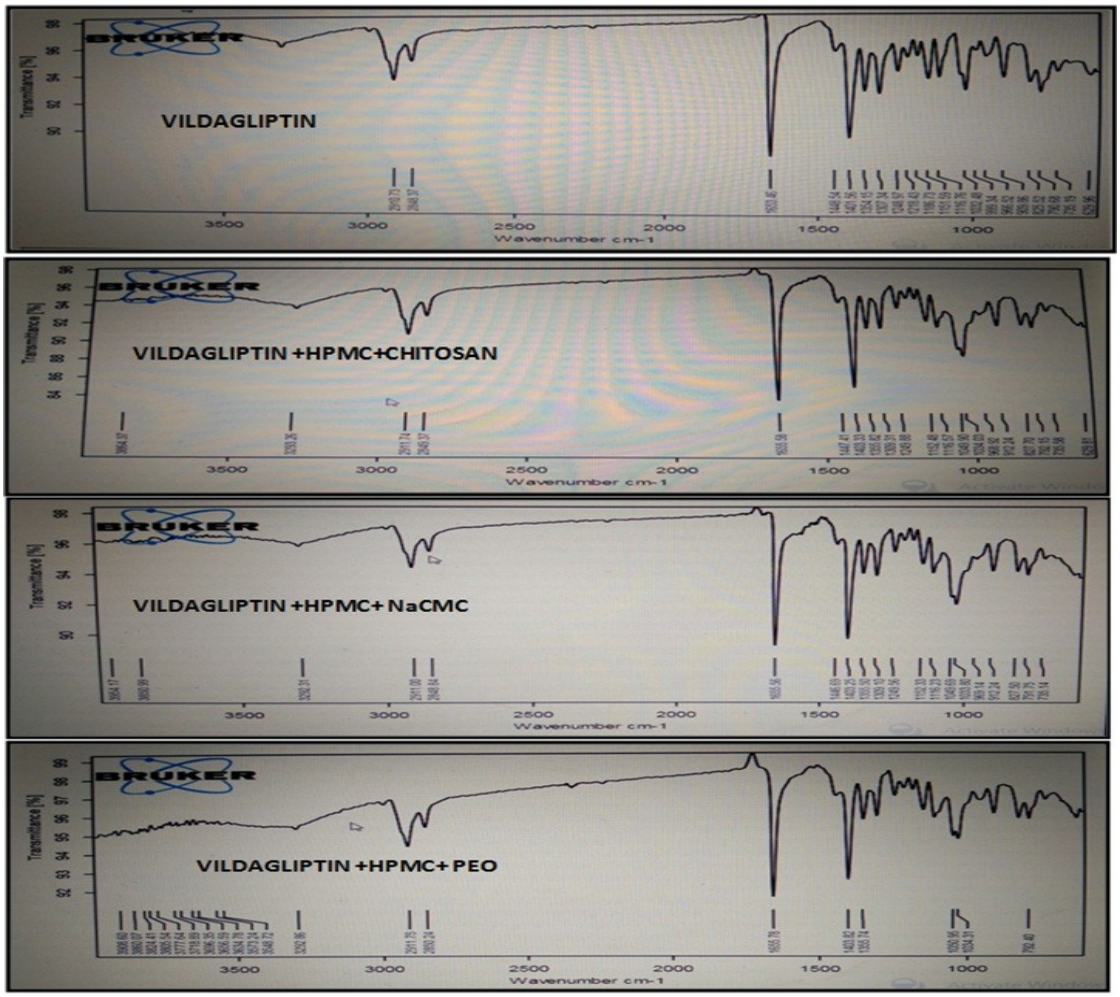

Figure 4:- Comparative FT-IR study of pure drug VDG, drug with ionic and non-ionic polymer physical mixtures.

The study of IST confirmed the physical stability of the drug with ionic and non-ionic polymers and other excipients at different conditions of temperature and a relative humidity of 75% ±5%. There was a very negligible amount of loss of drug in the drug-excipient mixtures after 3 weeks of storage under stressed conditions, and the residual drug content was found to be within the official limits. The results demonstrated that the model drug was compatible with each of the physical mixtures used for prototype formulation. The results of the IST study are presented in Table 2.

Table 2:- Results of IST after 3 Weeks of Storage at Stressed Conditions.

Samples	Ratio	Drug content of controlled samples (%)	Residual drug content of stressed samples (%)		
			25°C, 75±5% RH	35°C, 75±5% RH	45°C, 75±5% RH
Pure Drug (VDG)	------	100.81±0.72	101.78±2.47	99.53±1.13	98.71±1.23
VDG+HPMC	1:1	101.42±1.34	102.19±0.49	99.68±1.68	99.53±1.98
VDG+Chitosan+HPMC	1:1	100.73±1.82	99.95±2.31	99.96±0.63	99.91±2.68
VDG+CMC+HPMC	1:1	101.21±2.74	98.68±1.92	98.91±2.39	98.87±1.39
VDG+PEO+HPMC	1:1	100.84±1.92	98.81±1.22	99.37±0.98	98.68±2.41

Conclusion:-

FT-IR and DSC methods were used to study physical interaction of pure drug (VDG) with mixtures of ionic and non-ionic polymers. The combinations include hydroxy propyl methyl cellulose (HPMC K4M) with Chitosan and NaCMC with PEO as release retardant polymers for the investigation of extended release properties. DSC analysis revealed the characteristic peak transitions with minimal shift towards lower temperatures in the drug-polymer mixtures. FT-IR spectroscopic data seems to be consistent with the results obtained by the thermo-analytical method, offering complementary information about the functional moieties involved in such drug-polymer interactions. Results of the IST showed that there was no degradation of samples of pure drug, the drug polymer mixture, and other tablet excipients. In both DSC and FT-IR analysis, a weak intermolecular hydrogen-bond type interaction is incriminated. According to the spectroscopic data no other type of interaction can be proven, and does not rule out any structural change of the active pharmaceutical ingredients by hydrolysis, dimerization, complexation, condensation, etc. Therefore, based on the existing data, no real concern is formulated regarding the long-term stability of the proposed formulations. The relevance and implications of the existing hydrogen bonds between VDG and of such polymers over the pharmacokinetic properties of the formulation is yet to be proven.

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Conflict of Interest Declaration

The authors declare that they have no financial or nonfinancial competing interests related to the research work. The authors alone are responsible for the content and writing of the paper.

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