The following manuscript was accepted for publication in Pharmaceutical Sciences. It is assigned to an issue after technical editing, formatting for publication and author proofing Citation: Gholizadeh-Hashjin A, Shabani M, Monajjemzadeh F. Evaluation of pharmaceutical compatibility between acarbose and common excipients used in the development of controlled release formulations, Pharm. Sci. 2020, doi: 10.34172/PS.2020.67

Evaluation of pharmaceutical compatibility between Acarbose and common excipients used in the development of controlled release formulations

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Running title: compatibility between Acarbose and common excipients

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Abstract

Background: Excipients are used in the formulation of pharmaceutical dosage forms, but may interact with active pharmaceutical ingredients (APIs). Some of these interactions could alter the physicochemical properties of the APIs which can affect the therapeutic efficacy and safety. Acarbose is an anti-diabetic drug used in this study as an API to investigate its compatibility with common excipients in order to development of pharmaceutical controlled release formulations.

Methods: For this purpose, 15 different excipients were selected. Binary mixture of drug with each of the excipients (1:1 mass ratio) were prepared. Mixtures were analyzed immediately after mixing and also after incubation at stress conditions (adding 20% water and incubated at 40˚C for 2 months). The thermal analytical investigation like differential scanning calorimetry (DSC), Fourier transform infra-red spectroscopy (FTIR) and high-pressure liquid chromatography (HPLC) were employed for physicochemical evaluations of the possible incompatibility. PDA and Mass studies were performed to ensure the peak purity of the API HPLC peaks in stressed samples.

Results: Incompatible excipients with acarbose were determined as EC (ethyl cellulose), Carbopol 934, Hydroxypropyl cellulose, PEG2000 (Polyethylene Glycol 2000), Mg Stearate, Na Alginate and Poloxamer.

Conclusion: Results of this study would be used for the development of controlled release formulation of acarbose. It is recommended to avoid the use of incompatible excipients.
Key words: Acarbose, compatibility, controlled release, excipient, preformulation

Introduction

Acarbose is an oligosaccharide (Figure1) which inhibits α-glycosidase-hydrolase and α-amylase and decreases the absorption of glucose and consequently lowers blood sugar level. Acarbose is administered in 50-100 mg doses every 8 hours[1] and can cause poor patients' compliance.[2-4] So, acarbose is a suitable drug candidate in order to develop controlled release formulations to reduce the dosing frequency.[5]

Excipients selection and drug-excipient compatibility is a crucial stage in preliminary drug development process to formulate the safe, efficacious and stable drug product. However, there is no universally accepted protocol for this issue,[6,7] some techniques such as Differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR) and High-pressure liquid chromatography (HPLC) coupled with different detectors, are the most frequently used methods in compatibility studies.[6-9] Although DSC provides main physicochemical characteristics of a pure samples such as the melting point, it has been utilized in detecting drug and excipient compatibilities in mixtures.[10] It should be noted that, this technique provides an intermediate performance and should be used and interpreted carefully along with other instrumental results such as FTIR and HPLC.[11] In pre-formulation studies FTIR may also be applied to detect any changes in the absorption spectra of the drug-excipient blends. Thus it is necessary to get an in depth knowledge of the IR absorption pattern of the drug molecule and excipients.[12] Isothermal stress testing (IST) is another method which involves incubating the drug–excipient binary mixtures with or without moisture at high temperature for a certain time (e.g. 2 months) and determining the drug content by HPLC.[13] HPLC methodology creates a reliable final decision in drug-excipient compatibility evaluations.[6] This essential decision depends on a number of parameters such as accuracy and reproducibility of the used method.

To the best of our knowledge, the physicochemical compatibility of acarbose with pharmaceutical excipients has not been investigated yet. Thus drug-excipient compatibility was evaluated in this study using different techniques such as DSC, FTIR and HPLC.

Materials and Methods

Reagents and chemicals

Acarbose (CAS: 56180-94-0) was purchased from Hangzhou Dingyan Chem Co., LTD, China (purity = 99%) Excipients were all from Merck (Germany) with pharmaceutical grade (purity >97%). Names and CAS numbers of excipients are as follow:

Dextrose (CAS: 492-62-6), Sucrose (CAS:57-50-1), Lactose (CAS: 63-42-3), Dicalcium phosphate (CAS: 10031-30-8), Ethyl Cellulose (CAS: 9004-57-3), Eudragit E100 (CAS: 24938-16-7), Carbopol 934 cp (CAS: 9003-01-4), HPMC (CAS: 9004-65-3), Na Alginate (CAS: 9005-38-3), Hydroxy Propyl Cellulose 100000 (CAS: 9004-64-2), Sodium Carboxy Methyl Cellulose (CAS: 9004-32-4), Poly Ethylene Glycol 2000 (CAS: 25322-68-3), Poloxamer 407 (CAS: 9003-11-6), Magnesium Stearate (CAS: 557-04-0), Aerosil200 (CAS: 112945-52-5).

Excipients selection for preparation of controlled release formulation

List of investigated excipients in this study and their role in controlled release formulation is tabulated in Table 1[13] according to their pharmaceutical usage.

Preparation of Binary Mixtures

Binary mixtures of drug-excipients for IST were prepared by weighing the drugs and each of the excipients directly and then mixing them in a 1:1 mass ratio in 2ml micro tubes and then vortexing in order to get a homogenized mixture. Stress conditions were provided by adding 20% (v/w) water to the solid samples inside the micro tubes (200mg) and incubating at 40°C for 2 months. This an accepted procedure and was first introduced by Abu T M Serajuddin in 1999.[13,14]

Analytical methods

Differential Scanning Calorimetry

DSC curves were obtained in a Shimadzu DSC-60, and were analyzed using TA-60 software, in closed aluminum pans. Sample weight was kept constant at 5 mg and the heating rate was defined at 10˚C/min up to 300˚C under air atmosphere.

Fourier-Transform Infrared Spectroscopy

FTIR spectra was recorded to detect the possible incompatibility and the chemical reaction in incompatible mixtures. The IR spectra were obtained from each of the samples with FTIR Bomem (MB-100 series, Quebec, Canada) equipped with a software (GRAMS/32, version 3. 04) in the spectral range of 400-4000 cm^{-1}. KBr pellets were compressed using potassium bromide powder and solid samples in an approximate 10:1 mass ratio. The obtained IR spectra were the average of 10 consecutive scans.

High-pressure liquid chromatography

The Knauer HPLC system (Berlin, Germany) was made up of a Knauer controller quaternary pump and a UV detector (Knauer No. E 4310) and also a photodiode array detector (PDA) (Agilent, 1260 infinity). The whole operation was controlled using EZ Chrome elite software. The system was operated at a constant UV wavelength of 200 nm with a flow rate of 1ml/min by 20µL injection volume. The method was transferred[15] and validated according to ICH guidelines.[16] After reaching acceptable system suitability parameters, Linear range, accuracy, precision (repeatability), LOD and LOQ were calculated accordingly. The stationary phase was a high resolution C18 column (CLIPEUS, C18, 5µm, 250 × 2.1mm, USA) and the mobile phase was a mixture of acetonitrile and buffer solution (solution 0.35g/L disodium hydrogen phosphate and 0.6g/L potassium dihydrogen phosphate) in a 60:40 v/v ratio. Mobile phase was employed as a diluent for stock solutions of drug and consequent dilutions to prepare different calibration concentration of acarbose (100, 125, 250, 500, 1000µg/ml). Mixtures were analyzed immediately after mixing and also after incubation at stress conditions.[15,17] While analyzing stressed samples the purity of the peaks related to drug molecules were checked with PDA

technique. Peak identification was performed using Mass analysis. Mass spectrometric data were assessed using a Waters ZQ Mass 2000 (Waters, USA) spectrometer equipped with electron spray ionization and a single quadrupole Mass analyzer. All data were evaluated using Mass lynx version 4.01 software. Cone, extractor, and RF lens voltages, source and desolvation temperatures and cone and desolvation nitrogen gas flow were defined separately. Voltage values were set for Cone (3.5KV), capillary (90V), extractor (3V) and RF lens (1V), temperature was also defined for source (100°C) and desolvation (150°C) and gas flow rate was determined for cone (150L/hr) and desolvation (600L/hr) on the program.

Result and Discussion

In this section the DSC, FTIR, HPLC and Mass data for acarbose and its binary mixtures with excipients are illustrated and discussed.

Differential Scanning Calorimetry Results and discussion

Figure 2 depicts the DSC curves of drug, excipients and drug-excipient binary mixtures. In order to avoid chaos just incompatible excipients are shown. For the better illustration, scans related to pure drug, excipients and binary mixtures are shown separately. Peak melting temperature and enthalpy values of acarbose with different excipient mixtures are summarized in table 2.

Among 15 investigated excipients in this study, just 4 of them was found to be incompatible with acarbose based on DSC results. The melting endotherm of acarbose was unchanged in the rest of them, which could be assumed as drug-excipient compatibility.

Figure 2-A illustrates the DSC curves of pure acarbose along with pure excipients. DSC curve of acarbose shows the presence of an endothermic event at 221˚C, which can be related to acarbose melting accompanied by decomposition.[18-21]

Figure 2-B demonstrates the DSC curves of the binary mixtures of acarbose with incompatible excipients (PEG: Poly ethylene glycol, MgSt: Magnesium stearate, Eud: Eudragit, Na CMC: Sodium carboxy methyl cellulose).

DSC curve of PEG2000 shows the presence of an endothermic event in 53˚C caused by

excipient melting and an exothermic event in 278˚C.[12] The DSC curve of Mg St shows three endothermic and one exothermic event in 99˚C, 113˚C, 130˚C and 245˚C respectively.

In the DSC curves of acarbose -PEG and acarbose -Mg St binary mixtures, the endothermic peak of acarbose was disappeared. Furthermore, acarbose -PEG2000 binary mixture revealed a new endothermic peak at about 140˚C. These findings can be a sign of incompatibility.

The DSC curve of Eudragit shows the presence of an endothermic event at 189˚C which is caused by Eudragit melting phenomenon.[12] In the binary mixture of acarbose -Eudragit the melting endotherm of the drug and the excipient have been disappeared which can indicate the drug-excipient incompatibility.

The curve of Na CMC does not show any significant event except a broad endotherm at about 89.77˚C and an intense exothermic event beginning at about 280˚C. The loss of acarbose melting endotherm in the curve of the acarbose -Na CMC and the formation a new and small endotherm at 207˚C indicates a possible incompatibility of drug-excipient based on the DSC results.

It is difficult to find out the compatibility of some excipients with acarbose based on DSC finding. For example, the overlapping of the endothermic events of acarbose with EC in about 221˚C makes the compatibility judgment of the binary mixture of acarbose with EC almost impossible. In the case of acarbose - poloxamer the endothermic event of drug is overlapped with the exothermic event of the excipient and thus incompatibility cannot be distinguished. Due to the peak overlapping of the endothermic event of drug with excipient peaks, the thermal curve of acarbose -HPC and acarbose -Na Alginate could not predict the incompatibility or compatibility of the drug with these excipients (data are shown as a supplementary file named additional file 1).

Fourier-Transform Infrared Spectroscopy Results and discussion

FTIR is a complementary technique in this study and could assist to interpret the DSC results. Any change in the drug main absorption peaks in IR spectra of the stressed binary mixtures can be a sign of drug-excipient incompatibility.[9,22] In all binary mixtures, the presence of the acarbose main IR peaks was checked initially and then the formations or omissions of any new peaks were monitored in stressed mixture. Figure 3 illustrates IR spectra of pure standard

acarbose and its 1:1 (W/W) binary mixtures. Main IR peaks of acarbose as a pure reference standard powder have been interpreted in Table 3.

Only binary mixtures of incompatible excipients are shown in figure 3. Sign "Z" shows the spectra of the binary mixture immediately after mixing and thus at zero time, and sign "2" is showing the spectra after stress test for 2 months. A new sharp peak has been emerged between 1109-1032 cm^{-1} in the FTIR spectrum of the binary mixture of acarbose -Mg Stearate. acarbose -Na Alginate spectrum shows new peak at 1618 cm^{-1}. Acarbose-Eudragite displays a new peak at about 1732 cm^{-1}. In acarbose -EC a peak at about 1585 cm-1 has been removed. Acarbose-Carbopol shows three new peaks at 1019 cm-1, 1153 cm-1 and 1555 cm-1 respectively. Acarbose-HPC shows new peaks at 2141 cm-1. All these observations include emerging new peaks or loss of existing peaks and thus interpreted as a drug excipient incompatibility.

Based on the observations, unchanged main peaks of acarbose in binary mixture with dextrose, DCP, lactose, sucrose, HPMC, poloxamer, Aerosil, PEG2000 and Na CMC after stress test revealed that acarbose is compatible with these excipients based on FTIR results (data are shown as a supplementary file named additional file 2).

High-pressure liquid chromatography Results and discussion

The HPLC chromatogram of acarbose standard solution is depicted in Figure 4. Validation parameters are presented in Table 4. All stressed binary samples of acarbose were dissolved and injected into HPLC system. The percentage of the remaining drug after stress was calculated based on the calibration curve and data are depicted in Table 5. The drug loss less than 10 percent was estimated as a compatible mixture

Peak identification was done using photo diode array (PDA) and Mass detectors. Drug molecule peak had a purity factor greater than 0.997 and thus considered pure. Mass studies were performed to ensure the peak purity of the HPLC peak related to the main drug molecule in stressed samples. Mass spectra are illustrated in Figure 5 for acarbose. Figure 5-A displays the mass spectrum of acarbose in methanol (10 µg/ml). Molecular ion of the ($M+H^+$) could be seen at m/z equal to 646.7. This is accordance with molecular weight of acarbose, which is 645.6048 g/mol. Figure 5-B shows the mass spectrum of the HPLC peak related to acarbose in stressed binary mixtures. For preparing a uniform stress sample all mixtures were polled together to make a unique sample and this sample was analysed using mass spectrometry. The

molecular ion observed at 646.7 proves the peak purity.

According to Table 5, the incompatible binary mixtures of excipients with acarbose were associated to the excipients below:

EC, Carbopol, HPC, Na alginate, PEG2000, Mg Stearate and poloxamer. The least stable binary mixtures were determined as acarbose – PEG200 and acarbose - HPC with more than 50 % drug loss.

Cellulose derivatives such as EC and HPC, may contain reactive impurities which may interact with the drug molecule. It is known that peroxides, sugars and nitrite/ nitrate are the main impurities of these excipients. In addition, HPC may contain formic acid as organic acid impurity. Trichlormethiazide is a diuretic and can be an example of drug-HPC incompatibility.[23]

Polymerized excipients like PEG2000 and poloxamer may contain peroxides as well.[24] Ibuprofen,[25] Ketoprofen,[26] Phosphomycin[27] and Clopidogrel[28] are examples of PEG-drug incompatibilities available in the literature.

In a recent study it is shown that Na Alginate may increase hydrophilicity of the blends by addition of the functional groups of the alginate to them and may lead to stability problems.[29] Carbopol is chemically a polyacrylic acid and may have the potential to interact chemically with some drug molecules. The acidic nature of acrylic acid derivatives may be a cause of some interactions with active ingredients.[30] Mg Stearate incompatibility reasons are stated to be related to altering environmental pH and catalysing degradation.[24] Aspirin is a typical example of incompatible drug with Mg Stearate.[31] Many other examples are present in the literature.[30] Acarbose is likely to interact with these reactive impurities or the excipients themselves and this needs further detailed studies to show the exact chemical degradation pathway and revealing the interaction mechanism/mechanisms.

Comparison Table

Table 6 summarizes all DSC, FTIR and HPLC results. Data consistency in concluding the compatibility or incompatibility form all 3 techniques are shown in this table. According to results gained by three different techniques (DSC, FTIR and HPLC), 53% agreement and 20%

disagreement was determined between the HPLC data as a reference of the final judgment and a sophisticated accurate and time-consuming method with DSC data as a fast method. In about 26% of the cases, DSC was unable to predict drug-excipient compatibility or incompatibility. It should be noted that conclusions could not be made merely based on DSC results and the analyst should be careful in interpreting DSC data. Data obtained from HPLC and FTIR were more consistent (80%) and only 20% disagreement was seen based on Table 6.

Conclusion

In preformulation steps of pharmaceutical manufacturing DSC and FTIR can easily been used in evaluating drug-excipient compatibilities. DSC is not a preferred method and only gives limited data but FTIR is more reliable. HPLC remains the gold method in such evaluations and pharmaceutical chemists can use fast techniques as screening methods along with HPLC to reach the accurate results.

In this study drug-excipient compatibility of acarbose was studied with FTIR, DSC and HPLC methods. From a physicochemical viewpoint, the anomeric carbon in acarbose is free which makes it suitable to be incorporated in oxidation and reduction reactions. According to obtained data, acarbose was found to be compatible with HPMC, Aerosil, lactose, sucrose, Eudragit, dextrose, Na CMC and DCP. Incompatible excipients with acarbose were determined as EC, Carbopol, HPC, PEG2000 (Peroxide), Mg Stearate, Na Alginate and Poloxamer. It is recommended to avoid the use of incompatible excipient in the formulation of the acarbose dosage forms.

A new approach has been established which can be useful for industrial pharmacists in similar formulation processes. Based on the results, the sophisticated, accurate and time-consuming HPLC method was in a good and moderate agreement with FTIR and DSC data as fast screening techniques, respectively.

Acknowledgements:

This paper was extracted from Pharm.D thesis No. 3862 that was submitted to the Faculty of Pharmacy, Tabriz University of Medical Sciences and financially supported by the same university.

Conflicts of interests:

The authors declare no conflict of interest.

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Table 1. Excipients selection for a controlled release tablet preparation

Excipients category	**Used examples**
Filler-diluent	Dextrose – sucrose- lactose – DCP[1]
Coating agent	EC[2] - Eudragit
Release stablizer	Carbopol – HPMC[3]
Disintegrant	Na[4] Alginate
Binder	HPC[5] – Na CMC[6]
Lubricant	PEG[7]2000 – Poloxamer – Mg[8] stearate
Glidant	Aerosil

[1] DCP: Di calcium phosphate, [2] EC: Ethyl cellulose, [3] HPMC: Hydroxy propyl methyl cellulose, [4] Na: Sodium, [5] HPC: Hydroxypropyl cellulose, [6] CMC: Carboxymethyl cellulose, [7] PEG: Polyethylene Glycol, [8] Mg: Magnesium

Table 2. DSC results of peak temperature and enthalpy values of Acarbose and binary mixtures

Samples	**T_{Onset}/°C**	**T_{Peak}/°C**	**ΔH_f (J/G)**
Aca	262.25	278.96	**132.82**

Aca-PEG	215.11	248.31	**96.22**
Aca-PEG	47.7	52.03	**-56.76**
Aca-MgSt	90.91	101.13	**-97.82**
Aca-MgS	108.76	112.95	**-3.49**
Aca-MgSt	134.92	136.98	**-26.44**
Aca-MgSt	213.72	217.61	**-13.77**
Aca-Eud	197.55	211.84	**-8.94**
Aca-NaCMC	205.28	207.97	**-4.64**

Table 3. Main IR peaks of Acarbose in its pure reference standard powder

Interpretation	Observed peaks
-CH_3 bend	1451
Acetal Vibration	1153
Acetal Vibration	1006
O-H bond	3284
(1640-1550) N-H bending in secondary amines	1648
CH3 stretching	2887

Table 4. Validation Parameters of HPLC method for Acarbose

Calibration equation	Regression coefficient (r)	LOD (µg/ml)	LOQ (µg/ml)	Concentration (µg/ml)	Accuracy ± SD %	Repeatability (RSD %)
y = 14144 x+ 414002	0.999	20.21	60.63	125	99.15 ± 3.92	3.00
				250	104.34 ± 4.07	3.46
				500	100.12± 1.05	0.98

Table 5. The percentage of the remaining drug content after stress test in Acarbose binary mixtures

Samples	Remaining Percentage of Acarbose after stress
Acarbose	97.85 ± 0.67
Acarbose -EC	64.23 ± 0.82
Acarbose -HPMC	94.35 ± 9.97
Acarbose -Carbopol	67.31 ± 3.56
Acarbose -HPC	53.87 ± 1.47
Acarbose -Aerosil	91.15 ± 11.72
Acarbose -Lactose	93.17 ± 1.57
Acarbose -Sucrose	97.73 ± 4.93
Acarbose -Dextrose	98.17 ± 0.76
Acarbose -PEG 200	32.59 ± 5.92
Acarbose -Eudragit	91.83 ± 1.93
Acarbose -MgStearat	84.57 ± 1.06
Acarbose -Alginat	84.57 ± 3.52
Acarbose -Na CMC	99.63 ± 6.38
Acarbose -Ploxamer	85.32 ± 10.41
Acarbose-Dicalcium Phosphate	95.43 ± 3.52

Table 6. Summarization of DSC, FTIR and HPLC results consistency for drug-excipient compatibility of Acarbose

Samples	**Prediction of Compatibility**			**Agreement of results between used method**		
	DSC	FTIR	HPLC	DSC with FTIR	HPLC With DSC	HPLC With FTIR
S_1 Acarbose + EC	-	×	×	-	-	✓

S_2	Acarbose + HPMC	✓	✓	✓	✓	✓	✓
S_3	Acarbose + Carbopol	✓	×	×	×	×	✓
S_4	Acarbose + HPC	-	×	××	-	-	✓
S_5	Acarbose + Aerosil	✓	✓	✓	✓	✓	✓
S_6	Acarbose + Lactose	✓	✓	✓	✓	✓	✓
S_7	Acarbose + Sucrose	✓	✓	✓	✓	✓	✓
S_8	Acarbose + Eudragite	×	×	✓	✓	×	×
S_9	Acarbose + Dextrose	✓	✓	✓	✓	✓	✓
S_{10}	Acarbose + PEG2000	×	✓	××	×	✓	×
S_{11}	Acarbose + Mg stearate	×	×	×	✓	✓	✓
S_{12}	Acarbose + Na Alginate	-	×	×	-	-	✓
S_{13}	Acarbose + Na CMC	×	✓	✓	×	×	✓
S_{14}	Acarbose + Poloxamer	-	✓	×	-	-	×
S_{15}	Acarbose + DicalciumPhosphate	✓	✓	✓	✓	✓	✓

[1]compatipility: ✓

[2]incompatibility: ×

[3]intense incompatibility: ××

Legend for figures

Figure 1. Acarbose chemical structure

Figure 2. DSC curves of incompatible excipients with Acarbose. A: pure Acarbose and pure excipients. B: binary mixture of Acarbose with excipients. Aca: Acarbose, PEG: Poly ethylene glycol, MgSt: Magnesium stearate, Eud: Eudragit, Na CMC: Sodium carboxy methyl cellulose.

Figure 3. FTIR spectra of pure standard Acarbose and its binary mixtures with incompatible excipients (Aca: Acarbose, MgSt: magnesium stearate, Alg: sodium alginate, EC: Ethyl cellulose, CA: Carbapol, HPC: hydroxyl propyl cellulose). Z= zero time, initially; 2: after 2 months, after stressed sample.

Fig 4. HPLC chromatogram of Acarbose standard solution (250 µg/ml).

Fig 5. The mass spectrum of A) Acarbose in methanol with a concentration of 10 µg/ml and B) collected HPLC peaks related to Acarbose in stressed binary mixtures

Figures

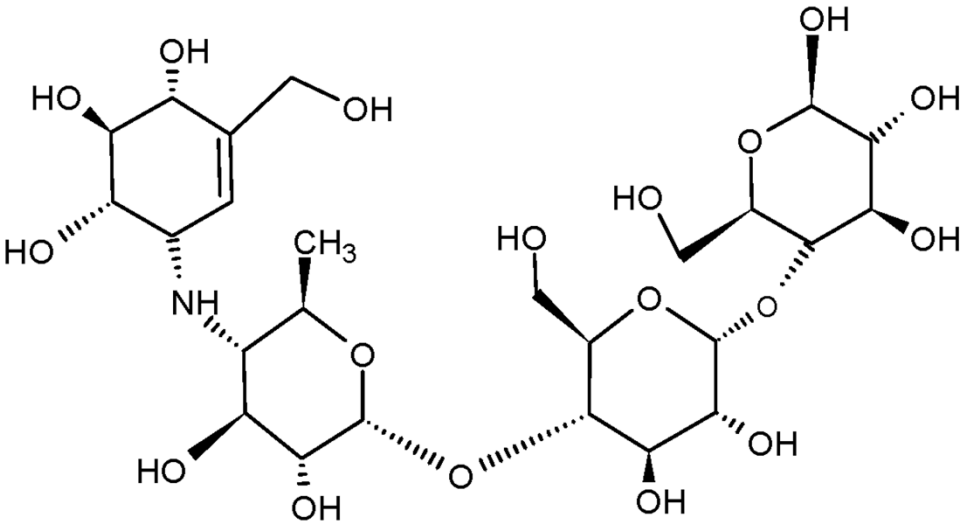


Figure 1

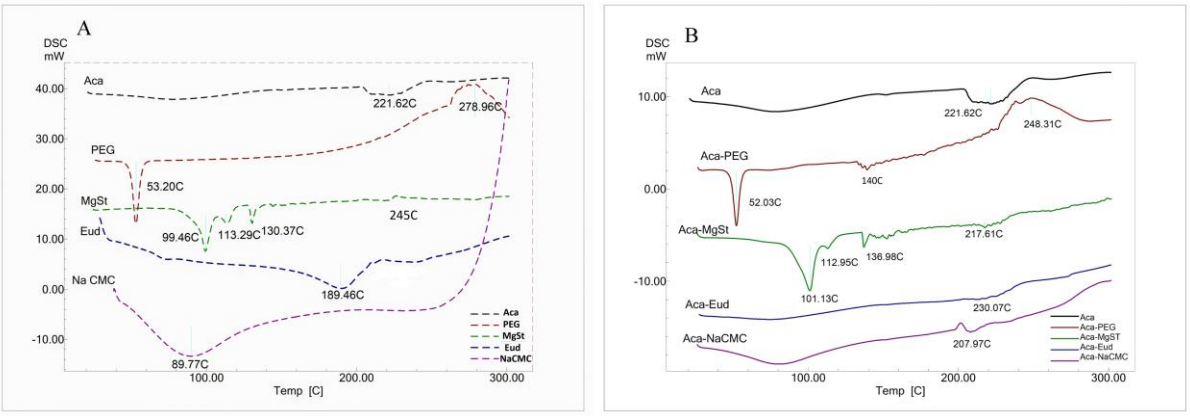
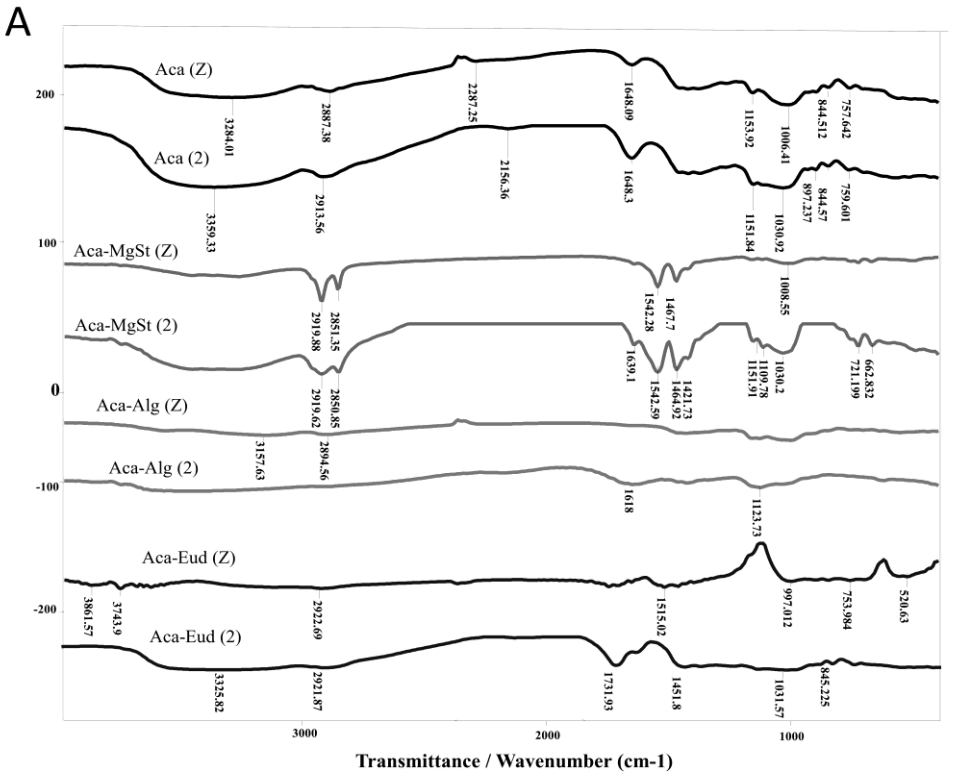


Figure 2.


A
Aca (Z)
Aca (2)
Aca-MgSt (Z)
Aca-MgSt (2)
Aca-Alg (Z)
Aca-Alg (2)
Aca-Eud (Z)
Aca-Eud (2)
Transmittance / Wavenumber (cm-1)

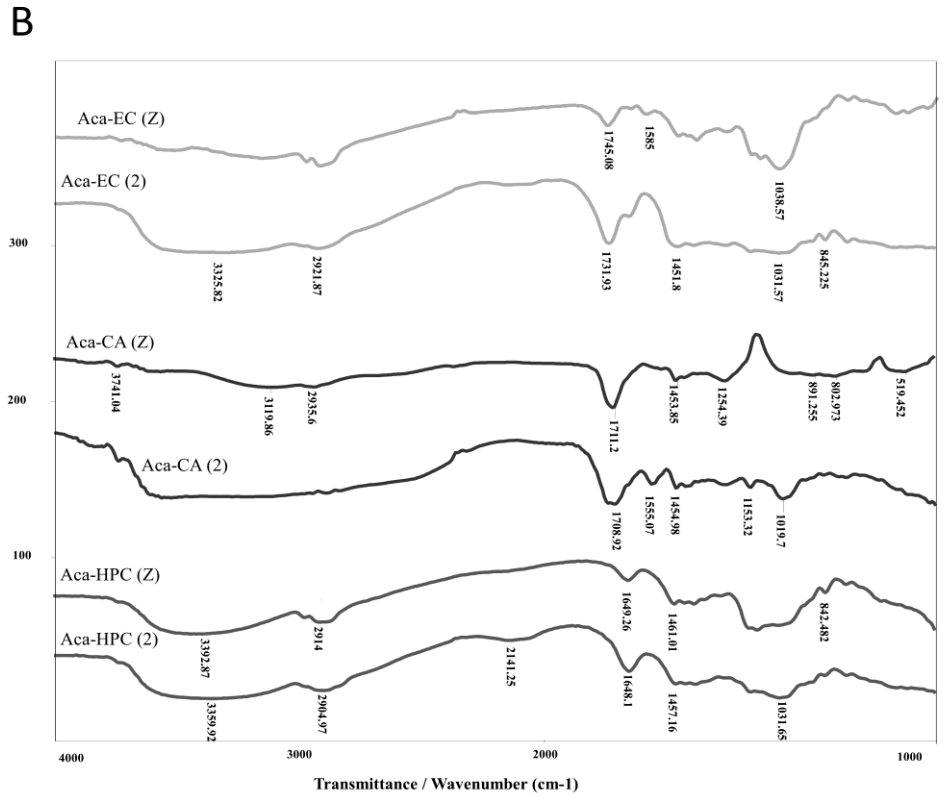

B
Aca-EC (Z)
Aca-EC (2)
Aca-CA (Z)
Aca-CA (2)
Aca-HPC (Z)
Aca-HPC (2)
Transmittance / Wavenumber (cm-1)

Figure 3.

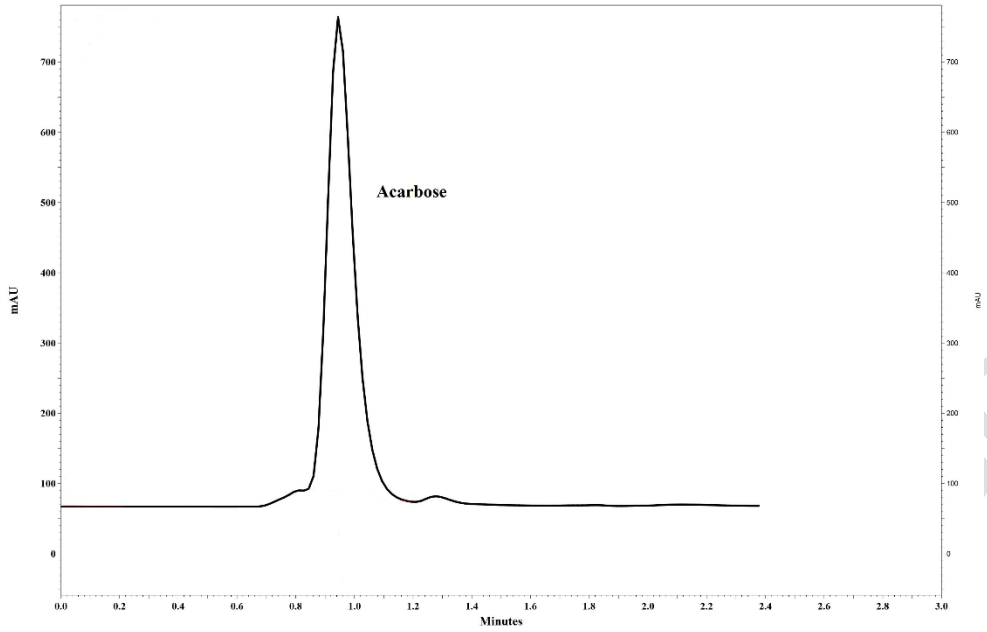


Figure 4.

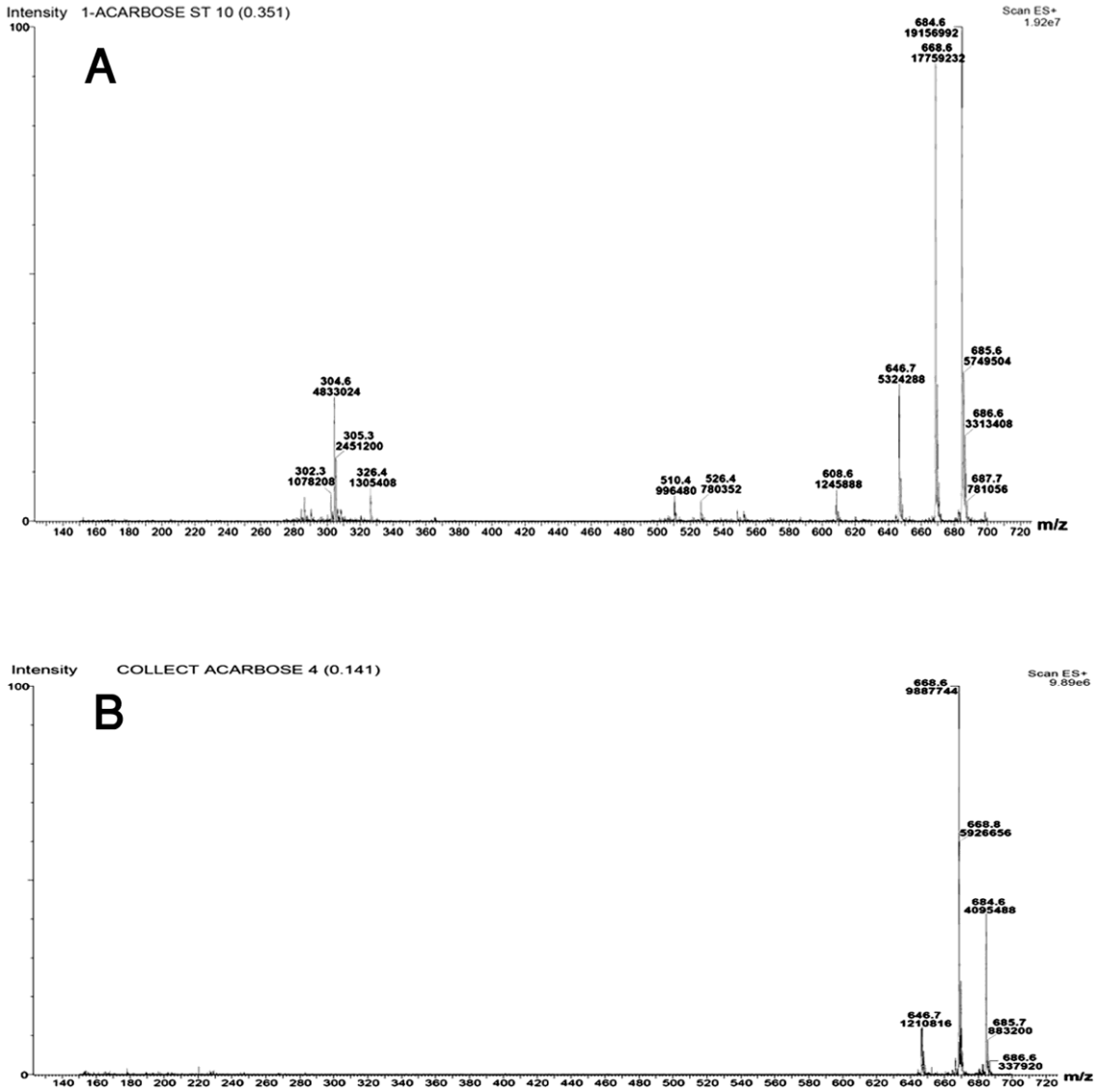
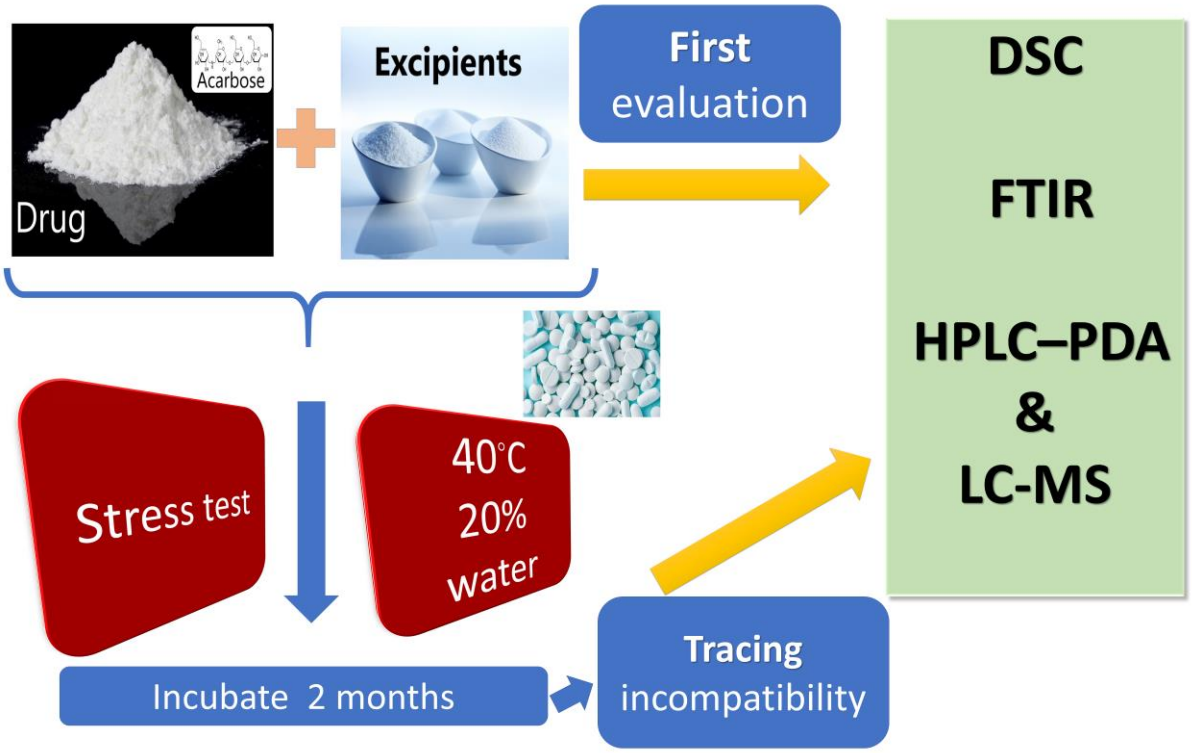


Figure 5.



Graphical Abstract.