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Drug-Drug Compatibility Studies of Novel Combination of Drugs for the Treatment of Irritable Bowel Syndrome

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ABSTRACT

Irritable bowel syndrome (IBS) has become a disorder of concern which affects the large intestine. Symptoms observed includes abdominal pain, cramping, bloating gas, and diarrhoea or constipation, or both. IBS is chronic and needs to manage for long term. Infection caused by bacteria or a virus needs to treat with an antibiotic and other relief of symptoms including intestinal discomfort, bowel disturbances and abdominal pain; are to be treated with antispasmodic. This, urged to design a new drug delivery system that would efficiently release Rifaximin and Pinaverium bromide, in a target specific site to lessen the adverse effects and dosing frequency, when administered in combination. However, certain combinations of drugs may pose safety concerns due to interactions. Thus, the current study was designed to evaluate the interaction of Rifaximin and Pinaverium bromide to develop a combo nano drug delivery system. Thermal stressing and characterization performed to evaluate the interactions of drugs in combination. Rifaximin and Pinaverium bromide combination shown to be stable without any significant physicochemical interactions. This study proved that Rifaximin and Pinaverium bromide is compatible with each other to develop nanoparticle formulations with combination of both drugs.

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INTRODUCTION

Rifaximin, 2S-Acetyloxy-5,6,21,23-tetrahydroxy-27-methoxy-2,4,11, 16,20,22,24,26-octamethyl-2,7 (epoxypentoeleca (1,11, 13) trienimino) benzofuro[4,5-e] pyride [1,2-a] benzimidazole-1,15(2H)-dione, is a non-systemic rifampin analogue and a site-specific antibiotic which targets gastrointestinal system (Al-Remawi, 2012; Zohri *et al.*, 2009). It showed several indications and used to treat travellers' diarrhoea caused by E. coli; hepatic encephalopathy recurrence; as well as diarrhoea-influenced irritable bowel syndrome (IBS-D) in adults of both sexes. Dosage for Travellers' diarrhoea: One 200mg tablet taken three times a day by oral route (Coco *et al.*, 2013; Viscido *et al.*, 2014). Dosage for Hepatic encephalopathy: by oral route one 550 mg tablet taken two times a day. The adverse effects associated with Rifaximin for treatment in travellers' diarrhoea ($\geq$ 5%): Flatulence, nausea, headache, abdominal pain, rectal tenesmus and defecation urgency. Most common adverse reactions in hepatic encephalopathy ($\geq$ 10%): Dizziness, flatulence, nausea, fatigue, ascites, headache and peripheral edema. Additionally, Rifaximin reported to have approximately 6 hours of mean elimination half-life, demanding adminis-

tered in multiple doses daily (Pichai and Ferguson, 2012; Antoniou *et al.*, 2015). Pinaverium bromide, 4-[(2-bromo-4,5-dimethoxyphenyl)methyl]-4-[2-(2-{6,6-dimethylbicyclo[3.1.1] heptan-2-yl}ethoxy)ethyl]morpholin-4-ium, atypical calcium antagonist and a quaternary ammonium compound that acts to restore normal bowel function. Therapeutically administered to get relief of symptoms associated (Moayyedi *et al.*, 2019) with irritable bowel syndrome (IBS) including abdominal pain (Gwee *et al.*, 2018; NICE, 2017; Chen and Wang, 2015), intestinal discomfort and bowel disturbances; and to treat symptoms related to functional illnesses of biliary tract. Dosage is 50mg tablet taken orally three times a day. The dosage maybe increased to maximal total daily dose of 300mg administered 100mg thrice a day. The adverse effects associated with Pinaverium treatment involve nausea, heartburn, distension, epigastric pain and/or fullness, constipation, and diarrhoea. Additionally, Pinaverium bromide reported to have approximately 1.5 hours of mean elimination half-life, demanding administered in multiple doses daily (Christen, 1995; Annaházi, 2014). This, urged to design and compound a new drug delivery system to effectively modify the release of Rifaximin and Pinaverium bromide, by reducing the dosing frequency and have lesser adverse effects.

However, certain combinations of drugs may pose interactions, leading to physico-chemical degradations. Physical interactions are those changes in the drug characteristics that do not form any chemical bond or break the drug structure, this can be identified by alterations in the organoleptic parameters. Chemical interactions are those changes in the chemical structure of the molecule which results in reduced drug content by formation of other molecule such as degradation products (Gupta and Saini, 2009; Venkatesan *et al.*, 2012; Lachman *et al.*, 1986). Physico-chemical interactions may cause safety concerns. Hence, mandatory thorough evaluation of drug-drug compatibility study is necessary. This study was focused to evaluate the interaction of Rifaximin (Shengjum *et al.*, 2007) and Pinaverium bromide to develop a combo nano drug delivery system (Ohwoavworhua and Adelakun, 2005; Carstensen, 1998; Venkatesan *et al.*, 2009).

MATERIALS AND METHODS

Rifaximin and Pinaverium bromide were procured respectively from Optimus Drugs, India and Jubilant Generics, India.

The HPLC grade water was prepared by using Evoqua water technologies, UK. All materials were of high purity grade and used without further purification.

Description

Visual observation of the test samples for any change in colour and texture and recorded.

Fourier Transform Infrared Spectroscopy (FTIR)

The samples were recorded for FTIR spectra in a Cary 630 Spectrometer (Agilent Technologies) using potassium bromide (KBr) disk technique (Backett and Stenlake, 2004; Ghoel *et al.*, 2005; Sudhamani and Kumar, 2010). Samples equivalent to 2mg of Pinaverium bromide, Rifaximin, and Pinaverium bromide + Rifaximin mixture were diluted with potassium bromide (about 100mg) respectively with glass mortar and pestle to compress disc. The samples were scanned after baseline correction against a blank KBr disc in the range of 4000–400 cm^{-1} wave number.

Differential Scanning Calorimetry (DSC)

The DSC thermogram of samples were recorded in a Q100 Differential Scanning Calorimeter (TA Instruments) using DSC aluminium sample pans. Samples equivalent to 50mg of Pinaverium bromide, Rifaximin, and Pinaverium bromide + Rifaximin mixture were placed in the aluminium sample pan individually and were scanned in the temperature range of 20–200°C (Saravanan *et al.*, 2004; Velavan and Venkatesan, 2016; Şengel *et al.*, 2006).

Water Content

Water content of samples were analysed by Karl Fischer titration method using 870 KF Titrino Plus (Metrohm AG). Samples equivalent to 100mg of Pinaverium bromide, Rifaximin, and Pinaverium bromide + Rifaximin mixture were tested individually for water content using a mixture of 1 volume of formamide and 2 volumes of methanol as the solvent.

Assay

Assay of Pinaverium bromide was measured by HPLC with WATERS Alliance e2695 equipped with Photodiode Array Detector 996. The separation was achieved with Symmetry C18, 150mm x 4.0mm, 3.5μm, No. 310. The elution was performed with mobile phase 1% triethylamine in water and acetonitrile (40:60), adjusted the pH to 3.5$\pm$0.05 using formic acid. Diluent is same as mobile phase. 1mL/min was the flow rate with controlled temperature at 28$\pm$2°C. PDA detector was set at the wavelength of 254nm and injection volume was 10μL for every samples and standard. Standard solution

Table 1: Thermal stress conditions, testing interval and Test parameters

Tests	Condition			
	50°C/75%RH Open	40°C/75%RH Open	30°C/75%RH Open	25°C/60%RH Open
Description	✓	✓	✓	✓
FTIR	✓	✓	✓	✓
DSC	✓	✓	✓	✓
Water content	✓	✓	✓	✓
Assay	✓	✓	✓	✓
Relates substances	✓	✓	✓	✓

Table 2: Description observations in Thermal stress conditions

Sample	Code	Description				
		Initial	50°C/75%RH Open	40°C/75%RH Open	30°C/75%RH Open	25°C/60%RH Open
Pinaverium bromide	PIN-AD0297	White to off-white powder	NVC	NVC	NVC	NVC
Rifaximin	RIF-A22142	Red-orange powder	NVC	NVC	NVC	NVC
Pinaverium bromide: Rifaximin (1:1)	PRCS0519	Orange powder	NVC	NVC	NVC	NVC

NVC: No Visual Change

Table 3: FTIR Samples

Sample No.	Sample Name
1	Pinaverium bromide 25°C/60%RH
2	Rifaximin 25°C/60%RH
3	Pinaverium bromide + Rifaximin 25°C/60%RH
4	Pinaverium bromide 30°C/75%RH
5	Rifaximin 30°C/75%RH
6	Pinaverium bromide + Rifaximin 30°C/75%RH
7	Pinaverium bromide 40°C/75%RH
8	Rifaximin 40°C/75%RH
9	Pinaverium bromide + Rifaximin 40°C/75%RH
10	Pinaverium bromide 50°C/75%RH
11	Rifaximin 50°C/75%RH
12	Pinaverium bromide + Rifaximin 50°C/75%RH

Table 4: DSC thermogram samples with endothermal peak temperature

Sample No.	Sample Name	Endothermic peak temperature (°C)
1	Pinaverium bromide 25°C/60%RH	166.19
2	Rifaximin 25°C/60%RH	62.00
3	Pinaverium bromide + Rifaximin 25°C/60%RH	61.94, 167.98
4	Pinaverium bromide 30°C/75%RH	166.13
5	Rifaximin 30°C/75%RH	61.46
6	Pinaverium bromide + Rifaximin 30°C/75%RH	54.00, 167.74
7	Pinaverium bromide 40°C/75%RH	166.43
8	Rifaximin 40°C/75%RH	67.93
9	Pinaverium bromide + Rifaximin 40°C/75%RH	64.69, 167.68
10	Pinaverium bromide 50°C/75%RH	165.95
11	Rifaximin 50°C/75%RH	76.22
12	Pinaverium bromide + Rifaximin 50°C/75%RH	64.03, 167.49

Table 5: Water content (%) values in different storage conditions

Tests	Condition			
	25°C/60%RH Open	30°C/75%RH Open	40°C/75%RH Open	50°C/75%RH
Pinaverium bromide	0.34	0.64	0.54	0.43
Rifaximin	5.99	4.35	6.38	6.39
Pinaverium bromide + Rifaximin	3.95	3.04	2.71	4.37

Table 6: Assay (%) values in different storage conditions

Tests	Condition			
	25°C/60%RH Open	30°C/75%RH Open	40°C/75%RH Open	50°C/75%RH Open
Pinaverium bromide	100.2	102.2	103.5	99.9
Rifaximin	98.2	97.3	93.2	92.7
Pinaverium bromide from Pinaverium bromide + Rifaximin mixture	102.2	100.5	99.4	97.5
Rifaximin from Pinaverium bromide + Rifaximin mixture	96.0	93.1	91.2	89.9

is prepared by weighing 50mg of Pinaverium bromide standard in a 100mL flask, dissolve with 30mL of diluent and make up the volume with the diluent. Test solution is prepared by weighing the sample equivalent to 50mg of Pinaverium bromide in a 100mL flask, dissolve with 60mL of diluent with shaking for 20min and make up the volume with the diluent. Assay of Rifaximin was measured by HPLC with WATERS Alliance e2695 equipped with Photodiode Array Detector 996. The separation was achieved with InerSustain C18, 250mm x 4.6mm, 5μm. The elution was performed with mobile phase buffer+solvent mixture (37:63), buffer is prepared with 3.16% ammonium formate in water, adjusted the pH to 7.2$\pm$0.05 using ammonia solution and solvent mixture is methanol: acetonitrile (50:50). Diluent is Acetonitrile-water mixture (40:60). 1.4mL/min was the flow rate with controlled temperature at 40$\pm$2°C. PDA detector was set at the wavelength of 276nm and injection volume was 20μL for every samples and standard. Standard solution is prepared by weighing 40mg of Rifaximin

Table 7: Related substances (%) values of Pinaverium bromide and Pinaverium bromide in Pinaverium bromide + Rifaximin mixture in different storage conditions

Main impurities (RRT)	Pinaverium bromide			
	25°C/60%RH Open	30°C/75%RH Open	40°C/75%RH Open	50°C/75%RH
Unknown (%) (RRT 1.255)	ND	0.05	0.06	0.05
Unknown (%) (RRT 1.320)	ND	ND	ND	0.05
Total (%)	0.00	0.05	0.06	0.10
Main impurities (RRT)	Pinaverium bromide in Pinaverium bromide + Rifaximin mixture			
	25°C/60%RH Open	30°C/75%RH Open	40°C/75%RH Open	50°C/75%RH
Unknown (%) (RRT 1.255)	-	-	-	-
Unknown (%) (RRT 1.320)	-	-	-	-
Total (%)	0.00	0.00	0.00	0.00

-: Not Detected

Table 8: Related substances (%) values of Rifaximin and Rifaximin in Pinaverium bromide + Rifaximin mixture in different storage conditions

Main impurities (RRT)	Rifaximin			
	25°C/60%RH Open	30°C/75%RH Open	40°C/75%RH Open	50°C/75%RH
Unknown (%) (RRT 0.494)	0.05	0.05	-	-
Unknown (%) (RRT 0.621)	0.06	-	0.10	0.16
Unknown (%) (RRT 0.642)	0.12	0.13	0.14	0.15
Impurity D+H (%) (RRT 0.761)	-	-	-	0.06
Total (%)	0.23	0.18	0.24	0.37
Main impurities (RRT)	Rifaximin in Pinaverium bromide + Rifaximin mixture			
	25°C/60%RH Open	30°C/75%RH Open	40°C/75%RH Open	50°C/75%RH
Unknown (%) (RRT 0.416)	-	-	-	0.07
Unknown (%) (RRT 0.429)	-	-	-	0.10
Unknown (%) (RRT 0.495)	0.05	-	-	-
Unknown (%) (RRT 0.621)	0.07	0.06	0.13	0.32
Unknown (%) (RRT 0.643)	0.12	0.12	0.15	0.26
Impurity D+H (%) (RRT 0.761)	-	-	0.05	0.10
Total (%)	0.00	0.00	0.00	0.00

-: Not Detected

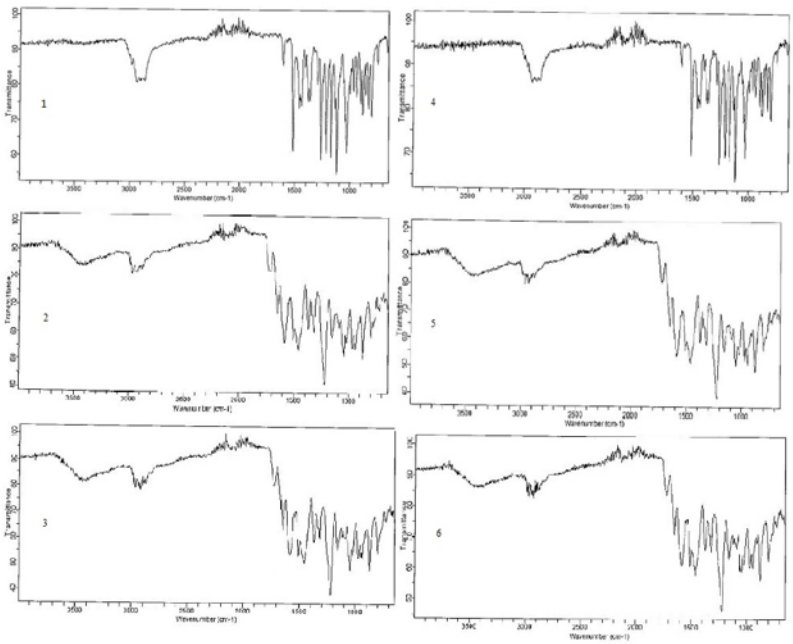

Figure 1: FTIR Chromatograms of Samples 1-6

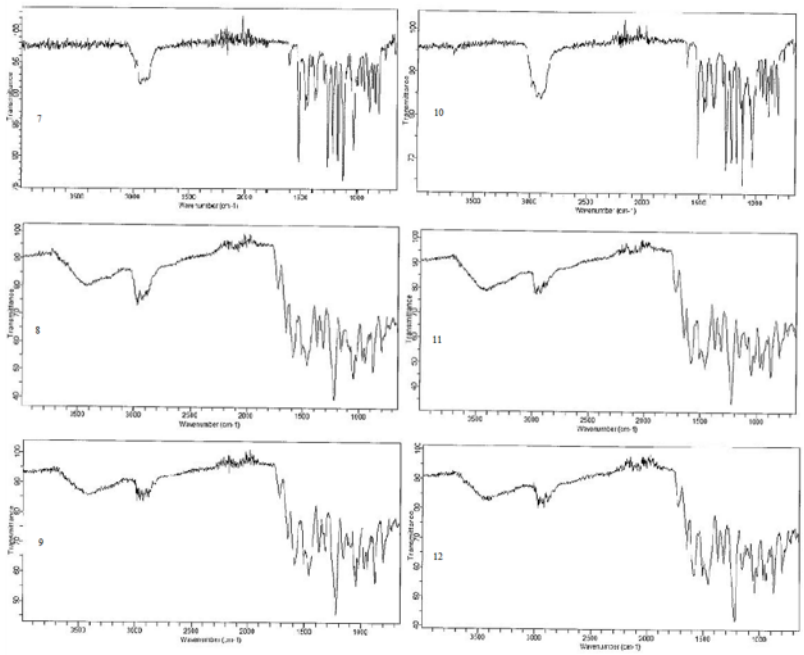

Figure 2: FTIR Chromatograms of Samples 7-12

working standard in a 100mL flask, dissolve with 50mL of diluent and make up the volume with the diluent, dilute 5mL of this solution to 50mL with diluent. Test solution is prepared by weighing the sample equivalent to 40mg of Rifaximin in a 100mL flask, dissolve with 50mL of diluent with shaking for 20min and make up the volume with the diluent, dilute 5mL of this solution to 50mL with diluent.

Related Substances

Related substances of Pinaverium bromide were measured by HPLC with WATERS Alliance e2695 equipped with Photodiode Array Detector 996. The separation was achieved with Symmetry C18, 150mm x 4.0mm, 3.5μm, No. 310. The elution was performed by Gradient with mobile phase A [0.5% triethylamine in water and acetonitrile (40:60), adjusted the pH to 3.5$\pm$0.05 using formic acid] and mobile phase B [0.5% triethylamine in water and acetonitrile (60:40), adjusted the pH to 3.5$\pm$0.05 using formic acid]. Diluent is same as mobile phase A. 1mL/min was the flow rate with controlled tem-

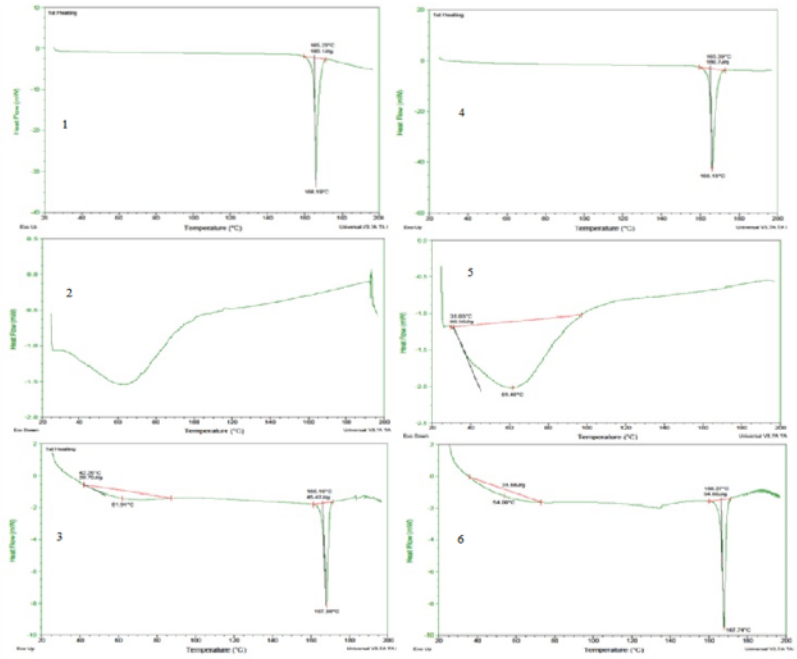

Figure 3: DSC Thermograms of Samples 1-6

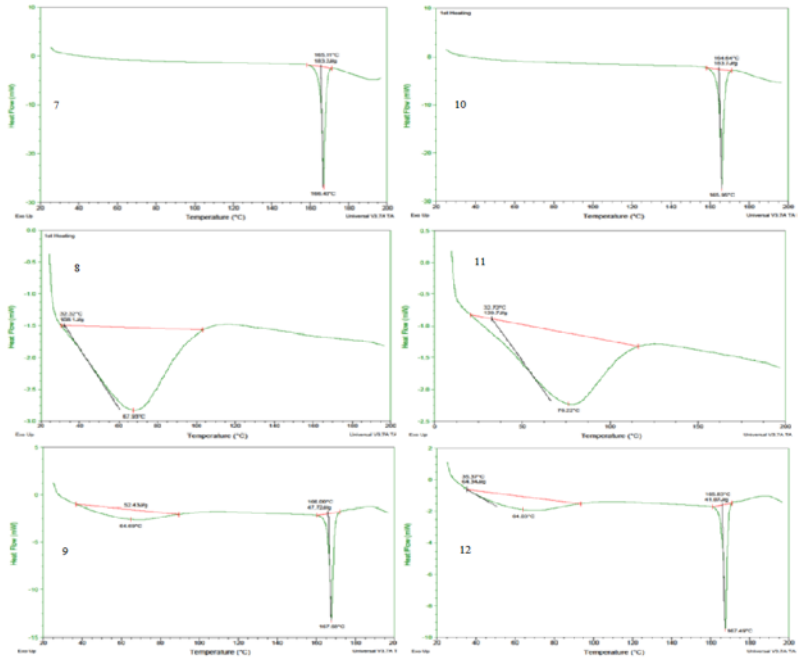

Figure 4: DSC Thermograms of Samples 7-12

perature at 28±2°C. PDA detector was set at the wavelength of 254nm and injection volume was 20μL for every samples and reference. Reference solution is prepared by weighing 5.0mg of each impurity A, impurity B and Pinaverium Br standard in a 100mL flask, and dissolve with mobile phase; dilute 5mL of this solution to 25mL with mobile phase. Test solution is prepared by weighing the sample equivalent to 100mg of Pinaverium bromide in a 50mL flask, dissolve with 20mL of mobile phase with shaking for 20min and make up the volume with the mobile phase. Related substances of Rifaximin was measured by HPLC with WATERS Alliance e2695 equipped with Photodiode Array Detector 996. The separation was achieved with InertSustain C18, 250mm x 4.6mm, 5μm. The elution was performed with mobile phase buffer+solvent mixture (37:63), buffer is prepared with 3.16% ammonium formate in water, adjusted the pH to 7.2±0.05 using ammonia solution and solvent mixture is methanol: acetonitrile (50:50), 1.4mL/min was the flow rate with controlled temperature at 40±2°C. Diluent is

Acetonitrile-water mixture (40:60). PDA detector was set at the wavelength of 276nm and injection volume was 20μL for every samples and reference. Reference solution is prepared by weighing 100 mg of rifaximin in a 20mL flask, add 1mL of 30% hydrogen peroxide solution, shaken and kept aside for 30min, and make up the volume with the diluent, 1mL of this solution was diluted to 50mL with diluent and then diluted 1mL of this solution to 10mL with the diluent. Test solution is prepared by weighing the sample equivalent to 40mg of Rifaximin in a 20mL flask, add 8mL of acetonitrile shaking for 20min and make up the volume with the water.

Experimental Studies

Thermal Stress Conditions and Sample Preparation

Samples for thermal stress testing were prepared in the ratio of Pinaverium bromide: Rifaximin (1:1). Individual drugs and the combined drugs samples were placed in the Espec constant climate chamber and followed In-house stress conditions as shown in Table 1.

RESULTS AND DISCUSSION

Samples were removed from the ovens after the stressing period and analysed for Description, FTIR, DSC, Water content, Assay and Related Substances.

Description

Description (appearance) of samples remained same without any visual changes during the storage period (Table 2). Hence, it is proved that the drug-drug combinations were physically stable.

FTIR Spectrometry

IR chromatograms of samples as shown in Table 3 are presented in Figure 1 and Figure 2. FT-IR spectrum of samples (1 to 12) with absorption bands which were characteristic and comparable with the absorption bands of an individual sample. Hence, it is proved that the drug-drug combinations were chemically stable.

Differential Scanning Calorimetry

DSC thermograms of samples as shown in Table 4 are displayed in Figure 3 and Figure 4. Pinaverium bromide illustrate an endothermal peak at around 165°C, while Rifaximin shows a broad endothermal peak between 40 – 100°C. It is obvious that Pinaverium Bromide melting point is stable under four different storage conditions. In contrast, in the case of Rifaximin, it looks that the temperature of the endothermic peak increases with increase in the storage temperature. In particular, Rifaximin stored at 25°C/60%RH exhibited endothermic peak at 60°C while Rifaximin stored at 50°C/75%RH endothermic peak was at 76°C. In the case of combination of Pinaverium Bromide and Rifaximin, both endothermic peaks were observed with Pinaverium peak being more intense. Hence, it is proved that the drug-drug combinations were chemically stable.

Water Content

Water content varies in different storage conditions which were comparable with individual sample and presented in Table 5. Hence, it is proved that the drug-drug combinations were physically stable.

Assay

Assay of individual drugs and drug mixtures are presented in Table 6. Assay results of drugs from drug mixtures were comparable with individual drugs. Hence, it is proved that the drug-drug combinations were chemically stable.

Related Substances

Related substances of individual drugs and drug mixtures are presented in Table 7 and Table 8. Related substances results of drugs from drug mixtures shows there is no any significant degradation in comparison with the individual drugs. Hence, it is proved that the drug-drug combinations were chemically stable.

CONCLUSION

The novel combination of Pinaverium bromide and Rifaximin proven to be stable without any significant physico-chemical interactions in the various tests performed in drug-drug compatibility studies at various stress conditions. Hence, this research proved that the Pinaverium bromide and Rifaximin are compatible with each other and this knowledge can be useful in developing modified-release nanoparticle formulations containing a combination of Pinaverium bromide and Rifaximin for the better treatment of irritable bowel syndrome (IBS).

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Conflict of Interest

The authors declare that there is no conflict of interest.

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