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ORIGINAL RESEARCH ARTICLE

In Vitro Stability and Recovery Studies of Pimavanserin in Water and in Different Vehicles Orally Administered

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Abstract

Background and objective Swallowing difficulties (i.e., dysphagia) occur in up to 40% of the adult general population, particularly among the elderly prescribed solid oral dosage forms. Pimavanserin is approved for the treatment of hallucinations and delusions in patients with Parkinson's disease psychosis (PDP) as a 34-mg capsule formulation. Patients with PDP may be at-risk for dysphagia that could affect administration of intact pimavanserin capsules. The stability of oral pimavanserin was evaluated in different liquid/soft food vehicles.

Methods The stability of pimavanserin intended for oral administration was assessed by sprinkling the contents of 1 pimavanserin 34-mg capsule into water (40 mL), applesauce (40 g), vanilla Ensure (60 mL), or non-pulp orange juice (60 mL).

Results The stability study demonstrated >95% recovery within 24 hours after contents of a 34-mg pimavanserin capsule were dispersed in applesauce, vanilla Ensure®, orange juice, or water. Assay values at 24 h for individual capsules were within 5% of time zero, and no significant change in the impurity profile was observed in any vehicle. Pimavanserin degradation products recovered from various food vehicles for individual and total degradation products were < 0.5% at all time points. In addition, the impurity profile of compatibility samples matched that obtained for a control sample.

Conclusion These results support the ability of pimavanserin to be given orally by emptying the capsule contents into soft foods or liquids in accordance with the product label.

Key Points

In vitro studies were undertaken with pimavanserin to evaluate its stability and recovery when administered orally in different liquid/soft food vehicles and in water.

Pimavanserin can be administered by emptying the capsule contents into applesauce, orange juice, vanilla Ensure®, or water and delivering orally.

Pimavanserin offers the flexibility to be administered using alternative vehicles to accommodate patient needs.

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1 Introduction

Swallowing difficulties (i.e., dysphagia) commonly occur in the general population, with up to 40% of adults experiencing problems [1, 2] and an increased incidence among the elderly [3, 4]. Among those requiring daily medications for chronic conditions, dysphagia may be especially critical because of difficulty swallowing oral dosage forms [1, 2, 5–7]. Studies show that the majority of individuals with dysphagia have difficulty taking oral medications [7]. Among community dwellers, 60% reported trouble swallowing pills; 68% opened a capsule or crushed a tablet because of swallowing difficulties, and 69% admitted missing at least one dose because of swallowing difficulties [8]. Those with chronic conditions, including Parkinson's disease, stroke, Alzheimer's disease, dementia, and other neurodegenerative conditions, are at especially high risk [3, 9–12]. Upwards of 80% of patients with Parkinson's disease experience difficulty swallowing solid oral dosage forms [13, 14].

Dosage form modification is common among those with swallowing difficulties [5]. Healthcare professionals often choose to empty the contents of the medication capsules

into water, applesauce, or another vehicle to administer the dose to those with swallowing difficulties in the absence of supportive information. However, before altering a dosage form for administration, it is important to determine any effects on drug stability or recovery using standard methodology to determine the in vitro stability and recovery of altered solid oral dosage forms [15]. For those who have difficulty swallowing solid oral doses, simply crushing a tablet or emptying a capsule into a delivery vehicle such as water or applesauce is not recommended without data to confirm stability of the drug in the vehicle [7, 16–18]. Altering the original formulation may affect the absorption, stability, and delivery of the drug and markedly alter its pharmacological effect [10, 17, 19, 20].

The US Food and Drug Administration recently issued a draft guidance for assessing stability of drugs in liquid and soft food matrices [21]. The draft guidance includes methodology to assess vehicle impact on product quality attributes. Pimavanserin is the active moiety of pimavanserin tartrate, it is freely soluble in water [21]. Pimavanserin is currently commercially available as 34-mg capsules and 10-mg tablets. The bioavailability of the pimavanserin oral tablet or capsule and pimavanserin solution is essentially identical [22] and can be taken orally with or without food [21]. Pimavanserin is approved as a capsule containing 34 mg of the active drug for the treatment of hallucinations and delusions in patients with Parkinson's disease psychosis. The population with Parkinson's disease psychosis typically is older and may be especially at risk for dysphagia, which could affect proper administration of pimavanserin [13, 14]. In vitro studies were undertaken to evaluate the stability of pimavanserin, in different liquid/soft food vehicles and in water. These data provide in use stability information with different liquid/soft food vehicles.

2 Methods

2.1 Chromatographic Procedure

The following chromatographic procedure was used for testing samples in stability (Table 1). The method was verified for being suitable for testing pimavanserin in the several vehicles. Table 2 provides a summary of the elements of validation performed.

2.2 Stability Study

The stability of pimavanserin intended for oral administration was assessed by sprinkling the contents of one pimavanserin 34-mg capsule into water (40 mL), applesauce (40 g), vanilla Ensure® (60 mL), or non-pulp orange juice (60 mL). Samples were tested at time 0, 2, 4, and 24 h after storage at ambient conditions.

Samples for assessment of assay (potency) stability of pimavanserin in vehicles were prepared as follows. Except for at time 0, samples were prepared for each subsequent time sampling in triplicate for each vehicle. The average ($n = 6$) accuracy/recovery results from the assay method verification were used as time 0. For each sample, one capsule was weighed. The content of the capsule was dropped into a 500-mL volumetric flask containing the vehicle, and the empty capsule shell was weighed and discarded. The flasks were gently swirled to ensure the capsule contents were visually incorporated within the vehicle. The flasks were kept on the bench at an ambient temperature for up to 24 h.

At the specified timepoint, approximately 450 mL of diluent (absolute ethanol) was added to the flask, and a stir bar was dropped into the flask. The samples were stirred vigorously for 2 h, and the flasks were left on the bench overnight. The next day, the flasks were sonicated for approximately 15–30 min. The stir bar was removed and rinsed carefully with diluent into the flask. The flask was diluted to volume with diluent and mixed well by inversion.

Samples for assessment of degradation products stability of pimavanserin in vehicles were prepared as follows. Four samples ($n = 4$) were prepared for each vehicle. For each sample, one capsule was weighed. The content of the capsule was dropped into a 50-mL volumetric flask, and the empty capsule shell was weighed and discarded. Five milliliters of each vehicle was added. The flasks were gently swirled to ensure the capsule contents were visually incorporated with the vehicle. The flasks remained on the bench at an ambient temperature for 2, 4, and 24 h, and time 0 samples were processed immediately. At the specified timepoint, approximately 45 mL of diluent was added to the flask, and a stir bar was dropped into the flask. The solution was stirred vigorously for 2 h, and the flask was left on the bench overnight. The next day the flasks were sonicated for approximately 30 min. The stir bar was removed and rinsed carefully with diluent into the flask, and the flask was diluted to volume with diluent and mixed well by inversion. The assay solutions were prepared by diluting the impurity solutions 1:10 with diluent.

3 Results

3.1 Stability Study

The stability study demonstrated the ability to deliver 34 mg of pimavanserin with > 95% recovery within 24 h after the contents of one pimavanserin 34-mg capsule were dispersed

Table 1 Chromatographic conditions

Component	Vehicles	Water via nastrogastric tube
Instrument	Agilent 1200 series, or equivalent	
Column	Waters XBridge C18, 5 µm 150 × 4.6 mm	
Mobile phase A	50 mM of ammonium bicarbonate, pH 8.0	
Mobile phase B	Acetonitrile/methanol, 80:20 (v/v)	
Flow rate	1 mL/min	
Injected volume	20 µL	60 µL
Autosampler temperature	5 °C	
Column temperature	40 °C	
Detection	UV at 210 nm	
Sample concentration (as free base)	Assay: 0.068 mg/mL Impurity: 0.68 mg/mL	Assay: 0.034 mg/mL Impurity: 0.34 mg/mL
Standard concentration (as free base)	0.068 mg/mL	0.034 mg/mL
PLOQ standard	0.05% of 0.68 mg/mL	0.05% of 0.34 mg/mL
SST solution	1% of 0.68 mg/mL (impurities: A, C, D, E, F, and G)	1% of 0.34 mg/mL (impurities: A, C, D, E, F, and G)
Diluent for standards	80/20 (v/v) ethanol/water	0.1 N HCl
Diluent for samples	Ethanol	0.1 N HCl
Run time:	40 min	
Example chromatograms	PLOQ: Fig. 1 SST solution: Fig. 2 Standard solution: Fig. 3	

Gradient method	Time (min)	Mobile phase A (%)	Mobile phase B (%)
	0.0	90	10
	30.0	0	100
	30.1	90	10
	40.0	90	10

min minutes, *PLOQ* practical limit of quantitation, *SST* system suitability test, *UV* ultraviolet

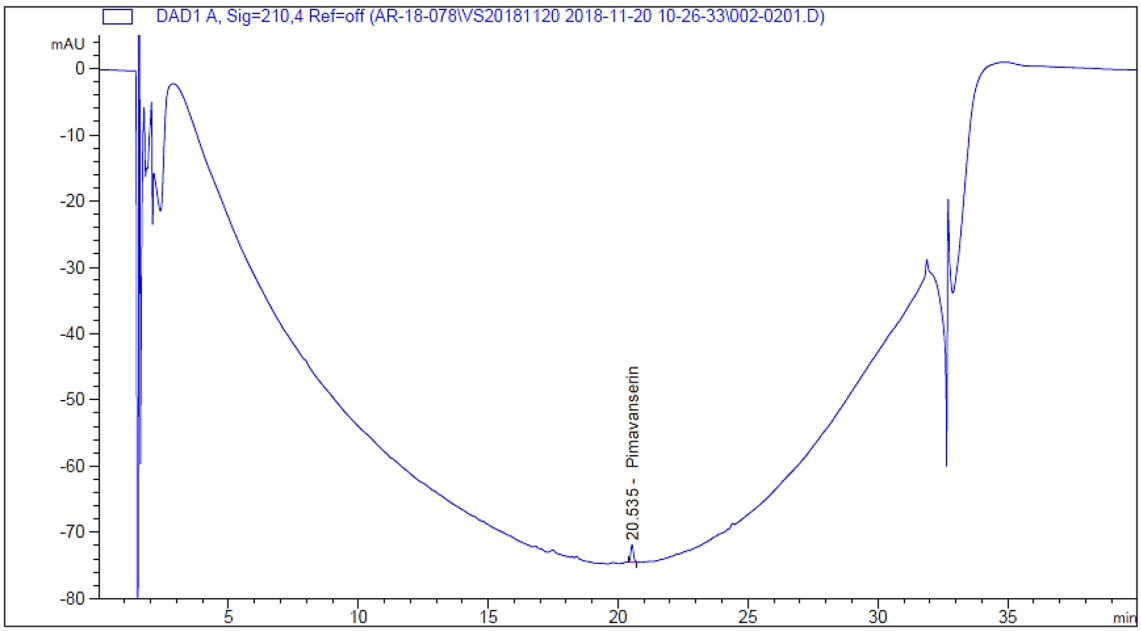

Fig. 1 Example chromatogram of the practical limit of quantitation at 0.05%

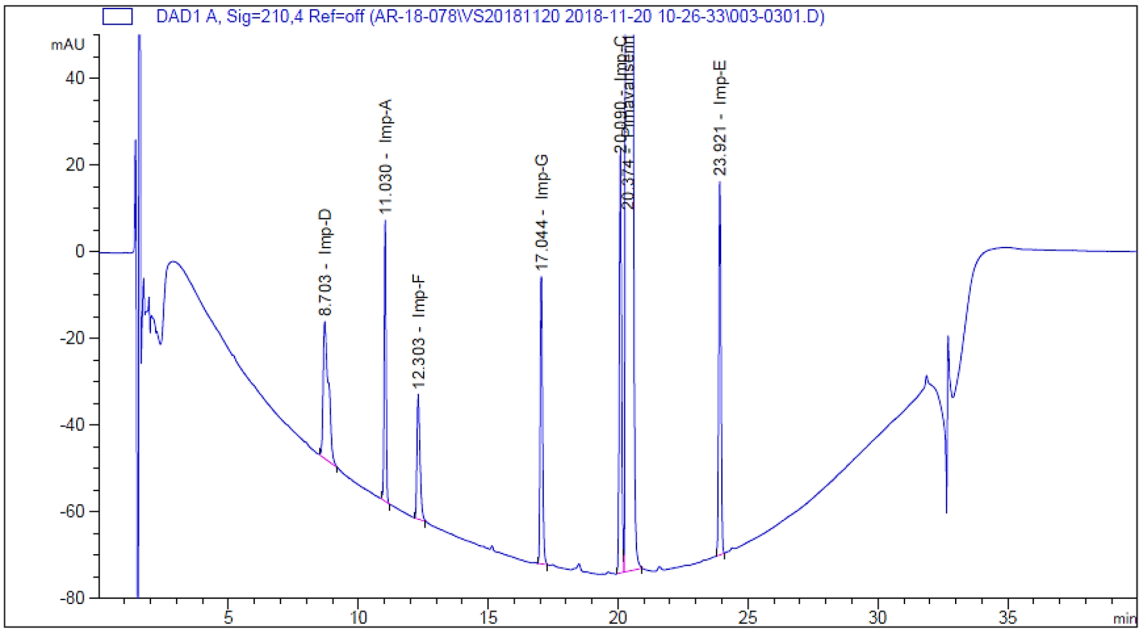

Fig. 2 System suitability test solution

in each of the vehicles, water, applesauce, vanilla Ensure, or orange juice (Table 3). Assay values up to 24 h for individual capsules were within 5% of time 0, and no relevant change in the impurity profile was observed in any vehicle except for apple sauce. An assay value of 96.3% was observed for applesauce after 24 h of storage, which differed from time 0 (101.9%) by 5.6%.

Stability results for pimavanserin degradation products recovered from various food vehicles for individual and total degradation products were consistent between all timepoints for each vehicle (Table 4). Two peaks related to vanilla Ensure were observed in the samples extracted at time 0 and did not change significantly during stability storage. All assay results were within 5% from time 0

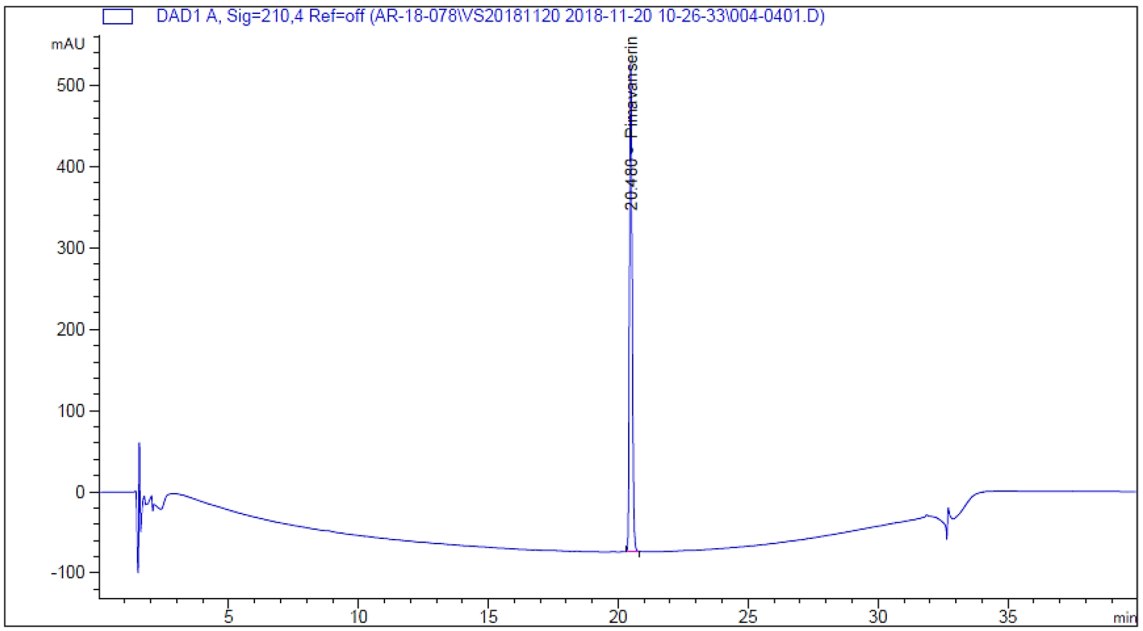

Fig. 3 Standard solution at 0.034 mg/mL

Table 2 Results summary for assay

Performance characteristics	Evaluated parameters	Target acceptance criteria	Results		
System precision	% RSD of peak areas and retention time from six injections of a standard preparation (0.068 mg/mL)	NMT 1.0%		RT (min)	Area
			%RSD	0.0	0.2
Actual capsules Accuracy/recovery at 100% level $N = 6$ for each food vehicle (assay)	For 34-mg capsules in each food vehicle: mean recovery ($n = 6$) assuming 100% of label claim	For each food vehicle: mean % recovery ($n = 6$) % recovery: 95–105%	Sample	Mean recovery (%)	RSD (%)
			Water	98.9	4.5
			Apple sauce	101.9	1.3
			Orange juice	100.3	1.2
			Vanilla ensure	100.0	1.7
Precision	RSD between assay values obtained from six independent sample preparations ($n = 6$, one capsule in each food vehicle, testing only assay)	RSD ($n = 6$) NMT 3%	See results in accuracy		
Linearity for vehicles: 0.048–0.093 mg/mL (70–130% of nominal concentration 0.068 mg/mL in 80:20 alcohol/water)	(1) Coefficient of determination (R^2) (2) Slope (3) Intercept	(1) NLT 0.998 (2) Record value (3) Record value	(1) $R^2 = 1.000$ (2) Slope: 42,619 (3) Intercept: 75		
Linearity for water: 0.045–0.00018 mg/mL (PLOQ: 130% of nominal concentration 0.034 mg/mL in 0.1 N HCl)	(1) Coefficient of determination (R^2) (2) Slope (3) Intercept	(1) NLT 0.998 (2) Record value (3) Record value	(1) $R^2 = 0.9996$ (2) Slope: 129898 (3) Intercept: 5.67		
Specificity	(1) Each food vehicle (2) Sample diluent	(1, 2) No significant interference	(1) See Figs. 4, 5, 6 and 7 (2) See Fig. 8		

NLT not less than, *NMT* not more than, *PLOQ* practical limit of quantitation, *RSD* relative standard deviation, *RT* retention time

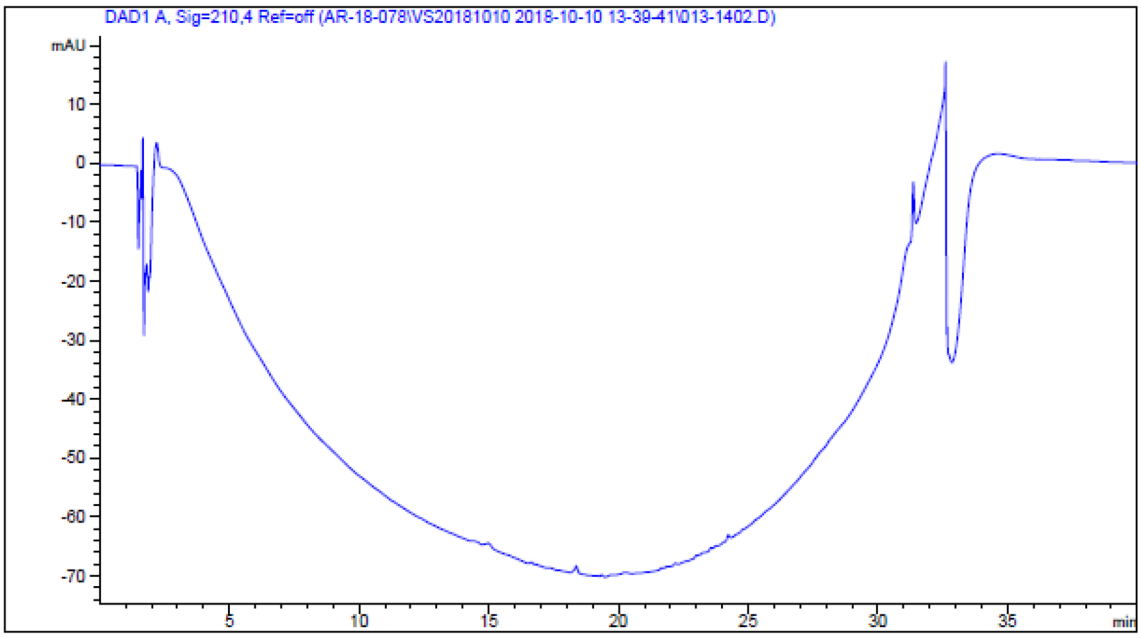

Fig. 4 Specificity: water assay blank

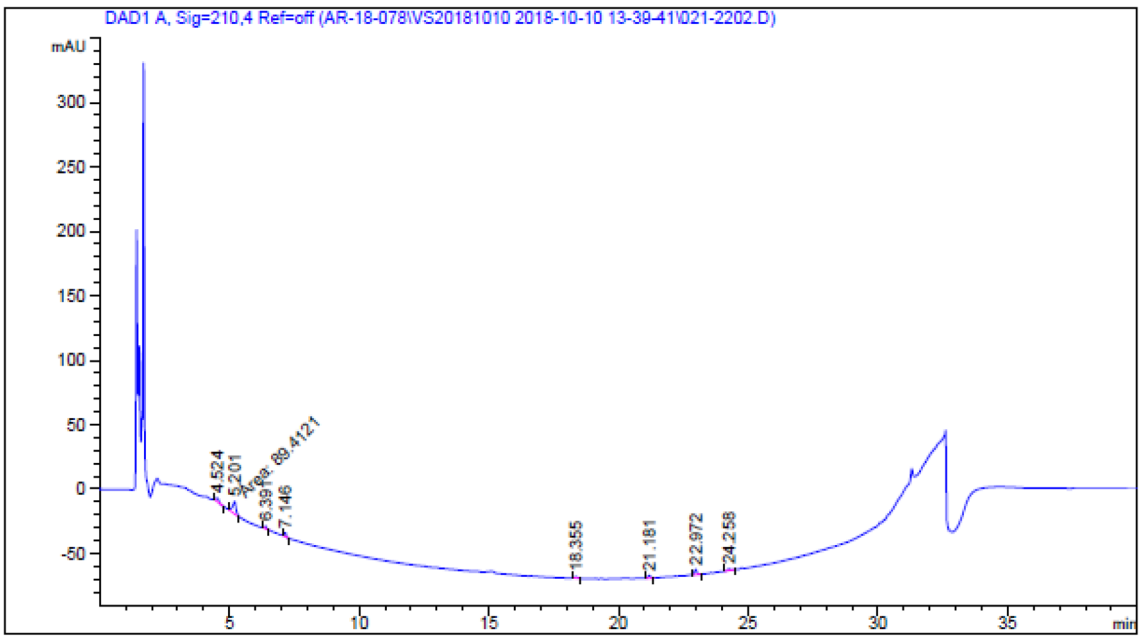

Fig. 5 Specificity: applesauce assay blank

and demonstrated an ability to deliver the expected dose (> 95% recovery) within 24 h at ambient room temperature after being dispersed in water, applesauce, vanilla Ensure, or orange juice (Table 5).

4 Discussion

Very low levels of unknown impurities (< 0.1%) were found in either the stability or recovery portions of the studies conducted here. The stability of pimavanserin in all vehicles was acceptable over 24 h at ambient room temperature.

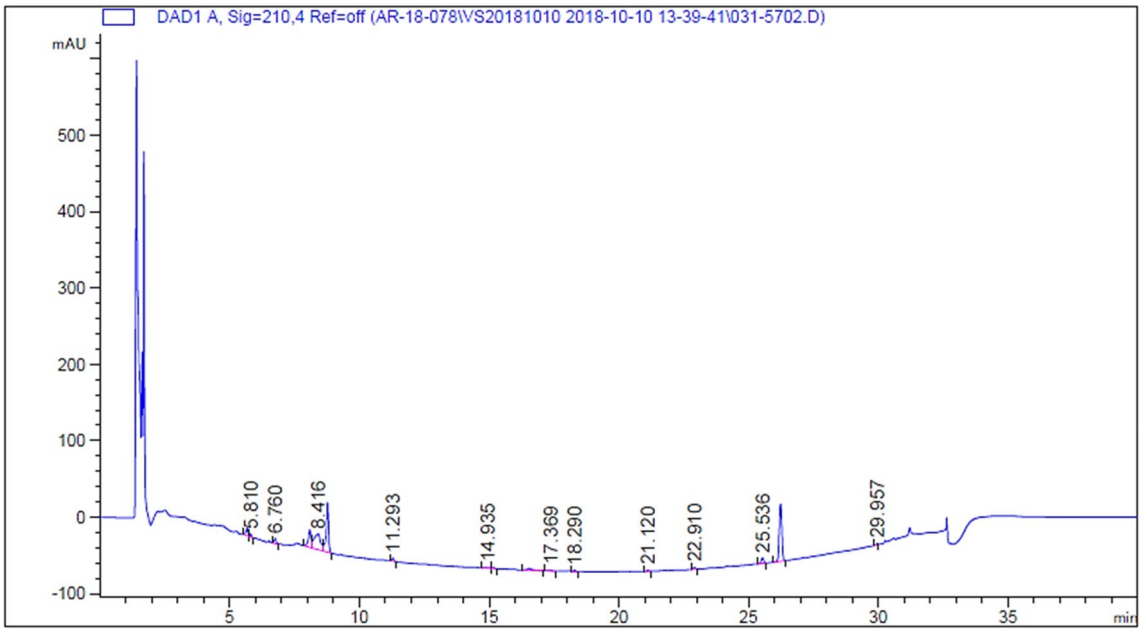

Fig. 6 Specificity: orange juice assay blank

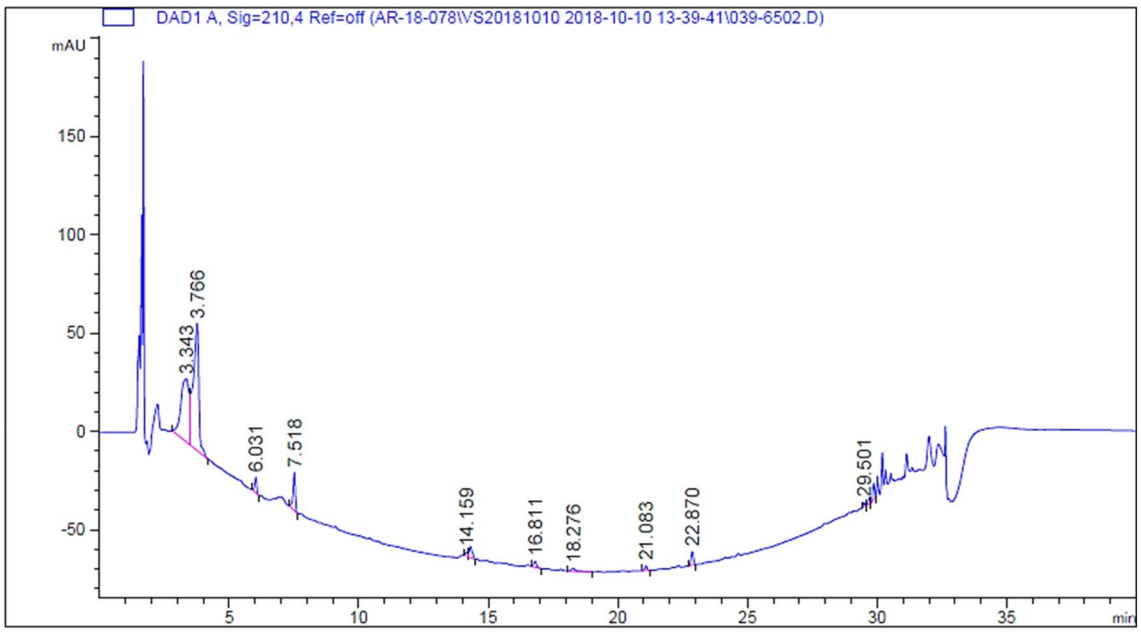

Fig. 7 Specificity: Ensure® assay blank

The consequences of crushing tablets or opening capsules for oral administration when not investigated for this method of administration can be serious for the patients. When the route of administration for a medication is changed, the pharmacokinetic properties can alter, specifically absorption, which could result in higher or lower systemic exposure and may render the treatment less well tolerated or less effective [7, 23]. The active ingredient released may

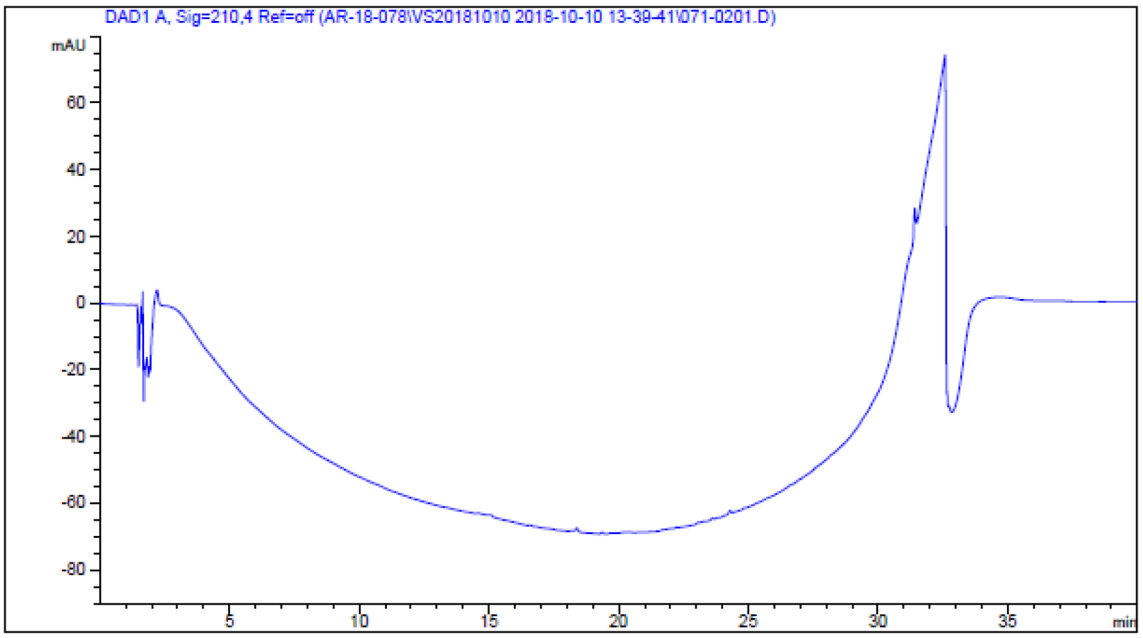

Fig. 8 Specificity: sample diluent ethanol

Table 3 In-use stability of pimavanserin from 34-mg capsules: assay study

Sample/time	Amount of vehicle	Assay (%) ($n = 3$)	Assay at time 0 (%) [$n = 6$]	Absolute difference from time 0 (%)
Water assay $T = 2$ h	40 mL	97.7	98.9	1.2
Water assay $T = 4$ h		95.6		3.3
Water assay $T = 24$ h		99.3		0.4
Applesauce assay $T = 2$ h	40 g	99.9	101.9	2.0
Applesauce assay $T = 4$ h		97.7		4.2
Applesauce assay $T = 24$ h		96.3		5.6
Orange juice assay $T = 2$ h	60 mL	99.2	100.3	1.1
Orange juice assay $T = 4$ h		98.0		2.3
Orange juice assay $T = 24$ h		98.3		2.0
Ensure assay $T = 2$ h	60 mL	100.3	100.0	0.3
Ensure assay $T = 4$ h		100.7		0.7
Ensure assay $T = 24$ h		98.1		1.9

h hours, *T* time

degrade on contact with light, moisture, or the vehicle used for administration [7].

The target patient population for pimavanserin, patients with Parkinson's disease psychosis, are typically older and have dysphagia as a consequence of Parkinson's disease, which often impacts swallowing solid oral dosage forms [13, 14]. This population of older patients with dysphagia most often have one or more chronic diseases in addition to Parkinson's disease and are taking multiple medications. Based on these results, pimavanserin capsule contents can be emptied and mixed into water, applesauce, orange juice, or vanilla Ensure without impacting the stability of the product.

Table 4 In-use stability for pimavanserin degradation products and impurities

Sample	Run time (min)	RRT	Impurity	$T = 0$ % w/w $n = 3$	$T = 2$ h % w/w $n = 3$	$T = 4$ h % w/w $n = 3$	$T = 24$ h % w/w $n = 3$
Water	8.98	0.44	Pimavanserin related peak 1	0.23	0.24	0.23	0.25
	20.06	0.99	Unspecified RRT 0.99	0.10	0.10	0.10	0.10
			Total	**0.33**	**0.34**	**0.33**	**0.35**
Applesauce	8.91	0.44	Pimavanserin Related peak 1	0.19	0.21	0.22	0.22
	19.95	0.99	Unspecified RRT 0.99	0.09	0.10	0.10	0.09
			Total	**0.28**	**0.31**	**0.32**	**0.31**
Orange juice	8.92	0.44	Pimavanserin related peak 1	0.17	0.17	0.17	0.17
	20.07	0.99	Unspecified RRT 0.99	0.09	0.09	0.09	0.09
			Total	**0.26**	**0.26**	**0.26**	**0.26**
Ensure	8.95	0.44	Pimavanserin related peak 1	0.22	0.20	0.23	0.23
	18.31	0.90	Ensure related peak	0.08	0.08	0.08	0.07
	20.06	0.99	Unspecified RRT 0.99	0.09	0.10	0.09	0.10
	22.29	1.10	Ensure related peak	0.06	0.05	0.06	0.06
			Total	**0.45**	**0.43**	**0.46**	**0.46**

h hours, *min* minutes, *RRT* relative retention time, *T* time

Table 5 In-use stability for pimavanserin: assay results from impurity samples study

Sample/time	Amount of vehicle	Assay (%)	Time 0 (%)	Absolute difference from time 0 (%)
Water assay $T = 0$	5 mL	95.6	98.9	3.3
Water assay $T = 2$ h		98.2		0.7
Water assay $T = 4$ h		97.1		1.8
Water assay $T = 24$ h		97.5		1.4
Applesauce assay $T = 0$	5 g	97.5	101.9	4.4
Applesauce assay $T = 2$ h		99.4		2.5
Applesauce assay $T = 4$ h		104.1		2.2
Applesauce assay $T = 24$ h		99.5		2.4
Orange juice assay $T = 0$	5 mL	97.7	100.3	2.6
Orange juice assay $T = 2$ h		97.5		2.8
Orange juice assay $T = 4$ h		96.4		3.9
Orange juice assay $T = 24$ h		99.2		1.1
Ensure assay $T = 0$	5 mL	97.1	100.0	2.9
Ensure assay $T = 2$ h		94.6		5.4
Ensure assay $T = 4$ h		97.9		2.1
Ensure assay $T = 24$ h		97.3		2.7

h hours, *T* time

5 Conclusions

Based on sufficient recovery and minimal degradation products observed for pimavanserin when mixed into vehicles and tested for up to 24 h, it can be concluded that:

- Pimavanserin can be administered by emptying the capsule contents into applesauce, orange juice, vanilla Ensure, or water and delivering orally.
- Pimavanserin offers the flexibility to be administered using alternative vehicles to accommodate patient needs.

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Declarations

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Conflict of interest YA, AB, and JN are employees of ACADIA Pharmaceuticals Inc., San Diego, CA, USA. VS provided consulting services under contract to ACADIA Pharmaceuticals, Inc.

Ethics approval The study included no human or animals and therefore this is not applicable.

Consent to Participate Not applicable.

Consent for Publication All authors approved submission of this manuscript.

Availability of Data and Material All relevant data are included in this manuscript.

Code Availability Not applicable.

Authors' Contributions AB: concept, design, conduct, analysis, interpretation, writing and approval of manuscript. YA: concept, design, conduct, analysis, interpretation, writing and approval of manuscript. VS: analysis, interpretation, and review and approval of manuscript. JN: review and approval of manuscript for submission.

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