

# Intrinsic stability and degradation pathways of bendamustine in injectable solution

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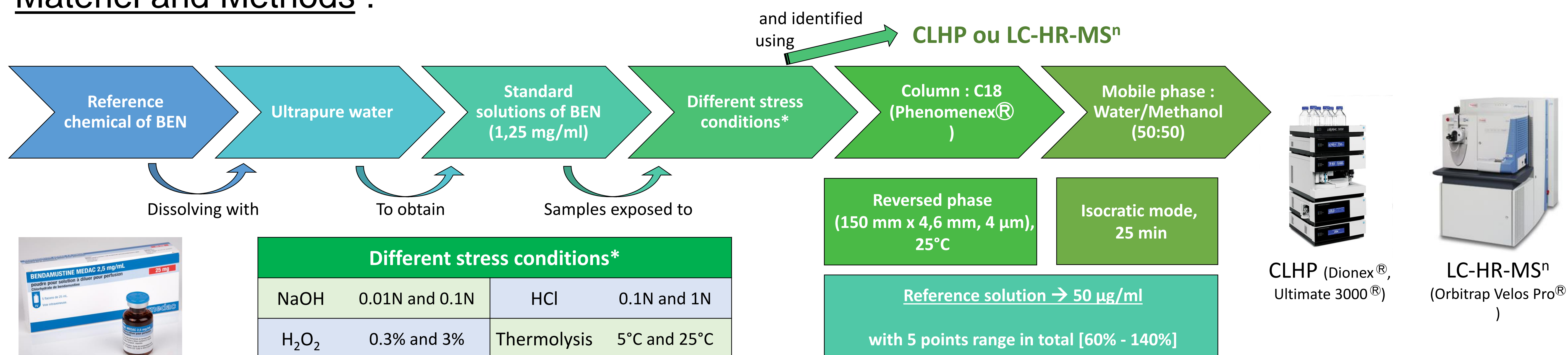
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## Introduction :

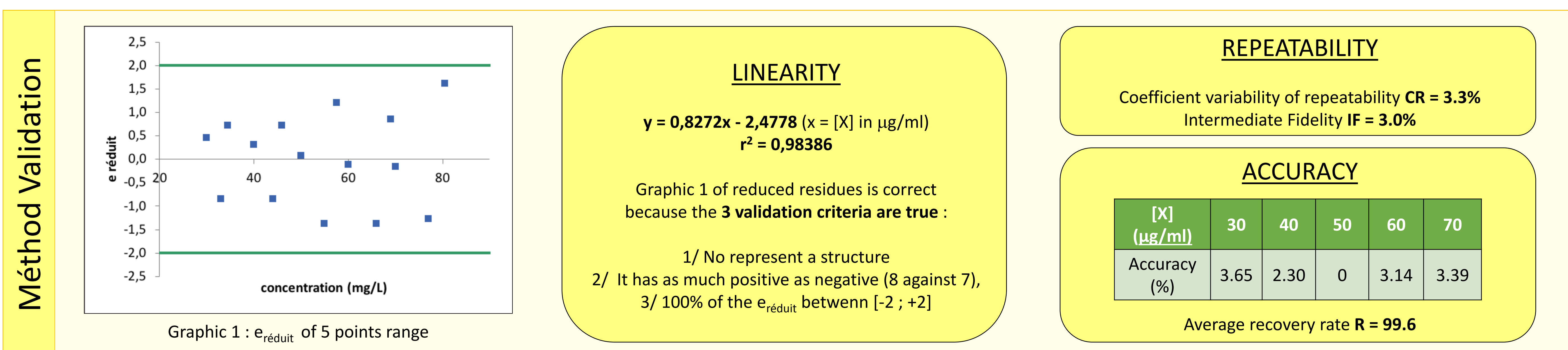
- Bendamustine (BEN)** is a chemotherapy medication used for the treatment of chronic lymphocytic leukemia (CLL), indolent B-cell non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM).
- The stability data provided by the manufacturer stated **8h at 4°C** for the lyophilized powder reconstituted with sterile water, **48h and 3h30** for the diluted solution in sodium chloride respectively at **4°C and 25°C**.
- As recommended by the International Council for Harmonisation (ICH), studies on a drug must be undertaken to establish the identification of its possible **degradation products (DP)** and for understanding the **intrinsic stability** of the drug molecule.

The **aim of this study** was the assessment of the **inherent stability characteristics of BEN** under different stress conditions by using Liquid Chromatography-Multistage Mass Spectrometry along with high-resolution Mass Spectrometry (LC-HR-MS<sup>n</sup>).

## Material and Methods :



## Results :



Fragmentation	Ionic mass observed (m/z)	Empirical formula	Exact theoretical mass (m/z)	Error (ppm)
BEN	358,1075	C <sub>16</sub> H <sub>21</sub> Cl <sub>2</sub> N <sub>3</sub> O <sub>2</sub>	358,1084	-2,4
A	340,0975	C <sub>16</sub> H <sub>19</sub> Cl <sub>2</sub> N <sub>3</sub> O	340,0978	-0,9
B	322,1314	C <sub>16</sub> H <sub>20</sub> ClN <sub>3</sub> O <sub>2</sub>	322,1317	-0,9
C	312,1024	C <sub>15</sub> H <sub>19</sub> Cl <sub>2</sub> N <sub>3</sub>	312,1029	-1,5
D	304,1207	C <sub>16</sub> H <sub>18</sub> ClN <sub>3</sub> O	304,1211	-1,4
E	276,1257	C <sub>15</sub> H <sub>18</sub> ClN <sub>3</sub>	276,1262	-1,8
F	268,1440	C <sub>16</sub> H <sub>17</sub> N <sub>3</sub> O	268,1444	-1,6
G	240,1491	C <sub>15</sub> H <sub>17</sub> N <sub>3</sub>	240,1495	-1,8
H	228,1135	C <sub>13</sub> H <sub>13</sub> N <sub>3</sub> O	228,1131	1,6
I	212,1179	C <sub>13</sub> H <sub>13</sub> N <sub>3</sub>	212,1182	-1,5
J	200,1180	C <sub>12</sub> H <sub>13</sub> N <sub>3</sub>	200,1182	-1,1

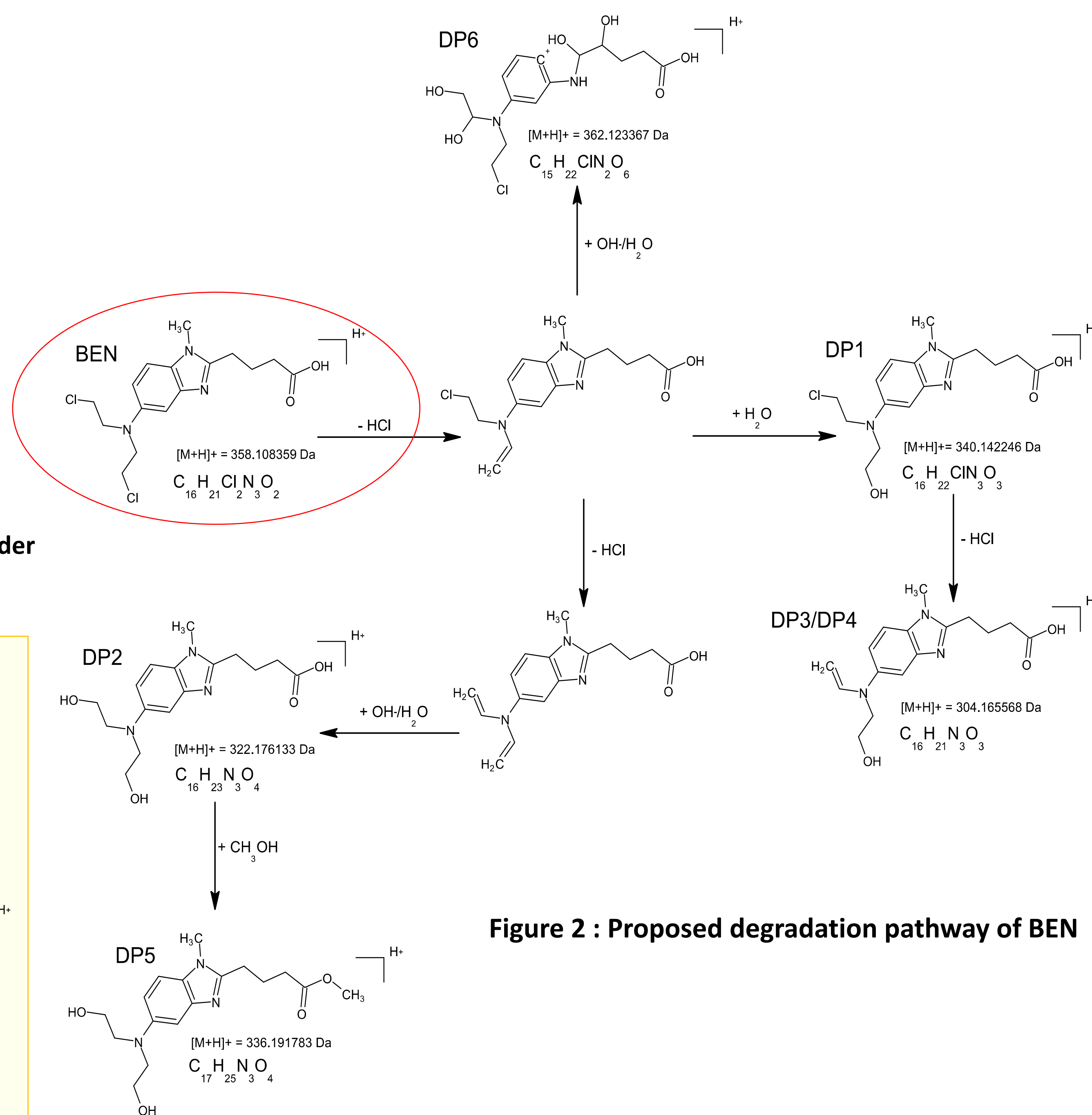
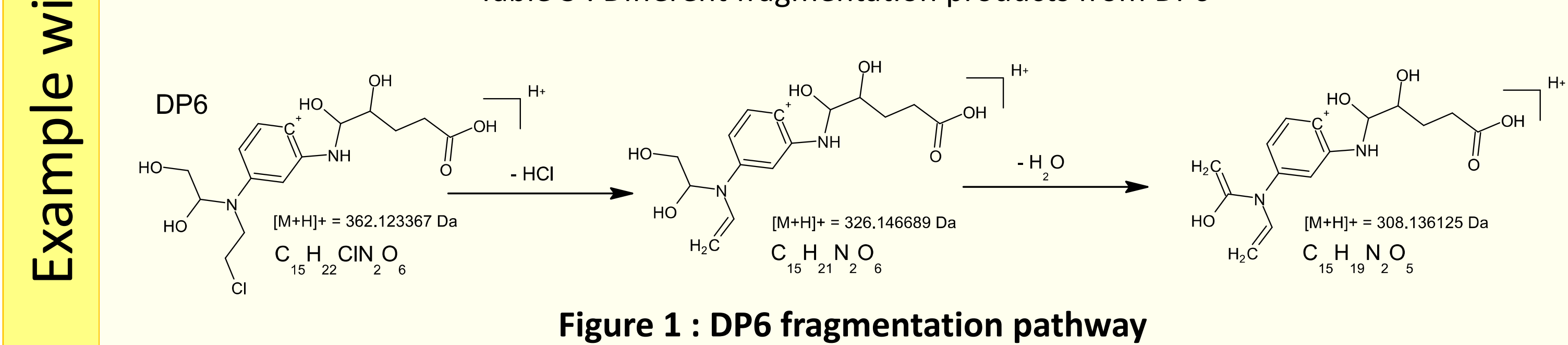
Table 1: Structures and HR-MS data of the major fragment ions of BEN

Produit	Condition de stress	Tr (min)
BEN	Toutes les conditions	12
DP1	Frigo T0	3,10
	Frigo J10	
DP2	T amb 30 min	1,72
	NaOH	
DP3	H <sub>2</sub> O <sub>2</sub>	1,56
	Frigo J10	
DP4	T amb 30 min (spe)	1,89
	NaOH	
DP5	Tamb 1h (pur)	1,89
	NaOH	
DP6	NaOH	2,7

Table 2 : Degradation products obtained under stress conditions and their retention time

Fragmentation	m/z	Ionic mass observed (m/z)	Empirical formula	Exact theoretical mass (m/z)	Error (ppm)
DP6	362,1	362,1224	C <sub>15</sub> H <sub>22</sub> ClN <sub>2</sub> O <sub>6</sub>	362,1234	-2,7
		326,1474	C <sub>15</sub> H <sub>21</sub> N <sub>2</sub> O <sub>6</sub>	326,1467	2,2
		308,1367	C <sub>15</sub> H <sub>19</sub> N <sub>2</sub> O <sub>5</sub>	308,1361	1,9

Table 3 : Different fragmentation products from DP6



## Discussion :

- BEN** → fragile under basic, hydrolysis, temperature and oxidative conditions.
- Based on the knowledge of its fragmentation pattern, up to **six degradation products (DP1 to DP6)** were highlighted suggesting that the degradation of BEN occur via multiple reaction pathways among which, hydrolysis, eliminations, nucleophilic additions or N-dealkylation.

## Conclusion :

- Understanding the **degradation pathways of BEN** was the key factor to mitigate the degradation of the drug product and help to anticipate its degradation.
- In view of the degradation of the reconstituted BEN solution, measures should be taken to ensure compliance to **good manufacturing practices** during the reconstitution, dilution, storage, transport and administration of the drug.
- Finally, the **absence of degradation product under acidic condition** has to be pursued to improve the drug stability.