Development of a stability indicating analytical by HPLC-Corona to perform ASAP studies and long term stability studies of a new potassium gluconate gel formulation

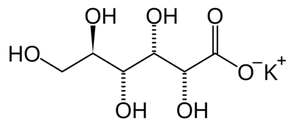
Boughanem C[1], Boccadifuoco G[1], Weck N[1], Wojcicki A[1], Boudy V [1,2], Goulay-Dufaÿ S[1]

1*: Agence Générale des Equipements et Produits de Santé (AGEPS), Assistance Publique – Hôpitaux de Paris (AP-HP), France*

2: Unité de Technologies Chimiques et Biologiques pour la Santé (UMR8258, Inserm U1022), Faculty of Pharmacy, Paris Descartes University, France

Introduction

Potassium gluconate is a gluconic acid's salt used as a potassium supplement. It is indicated for hypokalemia treatment. In this study, we performed a forced degradation study on this molecule and developed a stability indicating method to evaluate the degradation of potassium gluconate during long term stability study.



Potassium gluconate

Material & Method

Forced degradation conditions

Stress conditions	Liquid form	Solid form
Stressless	X	X
54°C – up to 21 days	X	X
84°C – up to 21 days	X	X
Photodegradation – up to 21 days	X	X
HCl 0,1M –up to 21 days	X	
NaOH 0,1M – up to 21 days	X	
H_2O_2 – up to 1 hour	X	
MMPP – up to 1 hour	X	
Fe^{2+} – up to 1 day	X	
Cu^{2+} – up to 21 days	X	

- Mass balance : content mass/mass (%) – sum of impurities. This difference should be around zero for the mass balance to be respected.
- Relative retention time (RRT) calculated according to the retention time of gluconate's peak.

Chromatographic conditions

- Column: Acclaim Trinity P2 (3 µm, 100 × 3.0 mm)
- Mobile phase: acetonitrile/ water/buffer ammonium formate 100 mM pH=3.5 (55/40/5, v/v/v)
- Time of run: 60 min
- Injection's volume : 20 µL
- Flow rate of 0.5 mL/min
- Column's temperature: 40°C
- Corona:
  - Evaporation's temperature: 55°C
  - Power function value: 1
  - Filter constant: 1 second
  - Data collection rate: 10 Hz

Validation criteria of a stability indicating method

- Retention factor (k) of gluconate: 2 < k < 10
- Limit of quantification (LOQ) < reporting thresholds of gluconate
- Pure peak of gluconate

Conclusion

The main stress factors found are oxidation and temperature. The stability indicating method developed allows a satisfactory resolution of gluconate from its degradation products and potassium.

Results & Discussion

Stress on solid form	54°C	84°C	Photo degradation
Content m/m (%)	93,05	90,93	90,18
Sum of impurities (%)	2,10	3,41	2,22
Mass balance (%)	-4,85	-5,66	-7,60
Number of impureties	3	3	3
RTT of 3 main impureties	0,13 (0,18%) 3,09 (1,45%) 3,25 (0,47%)	0,13 (0,62%) 3,09 (2,14%) 3,25 (0,65%)	0,13 (0,15%) 3,09 (1,59%) 3,25 (0,52%)

Table 1. Results of the forced degradation study on solid form

Two impurities are identified as critical impurities with RTT of 1.16 and 3.09. They are formed in thermolysis conditions (after 21 days at 84°C) and represented respectively 7.46% and 6.27% of gluconate's peak.

Stress on liquid form	54°C	84°C	Photo degradation	HCl	NaOH	Cu^{2+}	Fe^{2+}	H_2O_2	MMPP
Content m/m (%)	96,54	88,67	91,31	85,94	92,89	89,81	88,12	91,9	36,92
Sum of impurities (%)	9,08	16,28	4,52	Hydrolytic stress tests are inconclusive due to a superposition between gluconate's impurities and hydroxyd and chloride ion.		4,08	5,42	5,9	81,98
Mass balance (%)	5,62	-4,95	-4,17			-6,11	-6,46	-2,2	18,9
Number of impureties	5	5	4			4	6	5	4
RTT of 3 main impureties	0,09 (1,48%) 0,10 (1,55%) 3,09 (4,28%)	0,10 (1,68%) 1,16 (7,46%) 3,09 (6,27%)	0,10 (1,81%) 3,09 (1,95%) 3,25 (0,61%)			0,10 (1,07%) 3,09 (2,25%) 3,25 (0,48%)	0,10 (2,95%) 1,28 (0,89%) 3,25 (0,58%)	1,28 (0,75%) 2,98 (1,16) 4,55 (0,47%)	0,95 (49,30%) 4,27 (2,31%) 4,55 (28,80%)

Table 2. Results of the forced degradation study on liquid form

- All forced degradation conditions tested is closed to a degradation level between 5.0 and 20.0% of the active ingredient, except for the MMPP stress.
- On a quantitative side, mass balance isn't respected. This should be investigated further.
- On a qualitative side, 14 degradation products exceed qualification threshold fixed at 0.15% of active substance (ICH recommendations). However, not all of them are critical as they are unlikely to be formed during long term stability studies.
- The interferences related to hydrolysis conditions aren't an obstacle for the next studies because gel formulation is buffered at neutral pH.
- Liquid form of potassium gluconate is more prone to degradation than solid form.

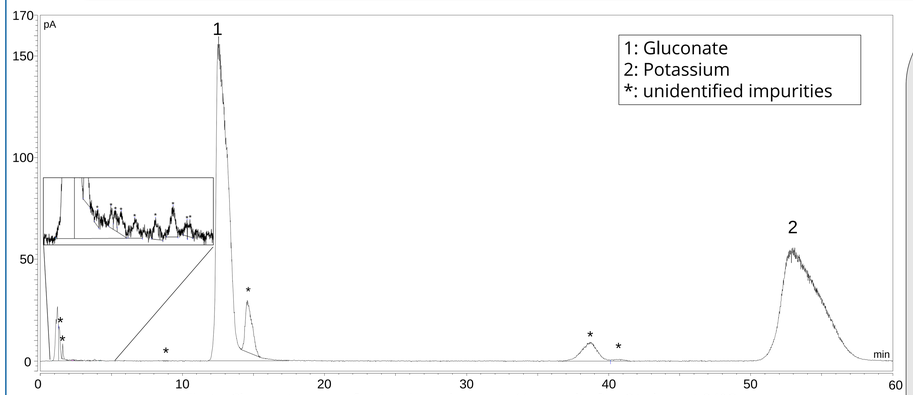


Fig.1 : Chromatogram of potassium gluconate (4 mg/ml) after 21 days at 84°C

- k (gluconate) = 6,6
- The LOD and the LOQ (2 and 8 µg/mL respectively) enable the detection of impurity at 0,05 % of gluconate (ICH recommendations).
- The resolution between majors impurities' peaks and gluconate's peak is acceptable (Rs ≥ 1,09) .
- The gluconate's peak is pure except for stress induced by MMPP. For this condition, the sample was overstressed which led to think that such impurities will not be formed during long term stability studies.