DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 18(13), 1449-1460 (1992)

EXPERIMENTING OSMOLALITY AS A CONTROL PARAMETER IN BINARY MIXTURES FOR PARENTERAL NUTRITION.

BARBIEUX A.

Service de Pharmacie,Hôpital E.Herriot, Place d'Arsonval, 69437 Lyon Cedex 03

MOULSMA M.

Laboratoire de Biochimie C, Hôpital E.Herriot, Place d'Arsonval, 69437 Lyon Cedex 03

SUMMARY

The authors consider using the osmolality (Em) as a control parameter in binary mixtures for parenteral nutrition that contains glucose, amino acids and electrolytes. The osmolality measurement is based on the freezing point depression according to the Raoult's law relation. For these mixtures, they study a relation between ideal Osmolality(iO) calculated by a micro-computer software and measured osmolality by using the ordinary least squares line technique. They validate upon the interval (8OO - 17OO) a linear relation :
Em = O.964 iO + 14.5O6 ; r = O.99. The authors conclude on the practical interest in using osmolality as a control parameter.

INTRODUCTION

In parenteral nutrition binary mixtures are manufactured with primary solutions : glucose, amino acids, electrolytes.Magesteries are more currently given few hours after their productions.The physico-chemical controls used for their validation must therefore resort to fast and easily applicable techniques. The measurement of osmolality (Em) based on the freezing point depression corresponds to these criteria. However it is difficult to use this parameter because of the problem met when calculating the theoretical osmolality of a complex solution. The objective of the present work is to validate an adequately precise method of determining the osmolality of binary mixtures in parenteral nutrition (BMPN) ; so as to define a value of reference for the control. Our approach to this issue is deliberately pragmatic in view of the quality control in pharmaceutical preparations.

ABSTRACTS

1-1 Osmolality measurement

Osmolality (Em) is an overall means to assess the contribution of different components of a solution in creating an osmotic pressure, in this very solution. In practice, this pressure is not measured directly. The measurement is based on; vapor tension or freezing point depression which are related to osmolality by physical laws. French pharmacopoeia advocates freezing point depression determination which is related to osmolality by RAOULT's Law (Fig 1).

1-2 Osmolality of simple solutions

For simple solutions , the osmolality (Fig.2) can be deduced from the concentration and the molal coefficient given in tables according to the concentration. The tables are different for each product. For electrolytes factor ν must integrate the dissociation coefficient. The molal coefficient (Φ) ranges from 0 to 1 and its value decreases as the concentration increases. It expresses the interactive forces between the ions and / or the molecules. The "ideal osmolality" (iO) is the value of the osmolality if value 1 is given to Φ. Experimentally iO represents nothing; it is not a measurable value. In opposition, osmolality Em is called "actual osmolality".

$$Em = \frac{DT}{1,858} \cdot 1000$$

Em = osmolality in milliosmoles per kilo water (mosm/kg)
ΔT = decrease of freezing point in degrees centigrades (C°)

Figure1: RAOULT'LAW

$$Em\ (mosm/kg) = \nu \cdot m \cdot \Phi = iO \cdot \Phi$$

ν =1 for inionised solutes
ν = number of pre-existing ions or ions formed by solvolysis from a molecule
m = molality in millimoles per kilo solvant
Φ = molal coefficient
iO = ideal osmolality

Figure 2 : OSMOLALITY OF SIMPLE SOLUTIONS

1-3 Osmolality of complex solutions

For solutions containing several products, it is practically impossible to set up tables that give Φ based on the concentrations; and therefore to predict the "actual osmolality". However, an "ideal osmolality" can be calculated according to the formula in Figure 3.

MATERIAL AND METHOD

2-1 Material

The osmolalities were measured by using an osmometer(Advanced Instrument Model 3D2). The production of the cold calories is done by the Pelletier effect. A thermometer is used as measure catheter.The freezing point is determined on the defreezing plateau. The apparatus

$$iO\ (mosm/kg) = \frac{\sum_{i=1}^{n} \nu_i . M_i}{\sum_{i=1}^{n} water_i}$$

ν_i =1 for inionised solutes

ν_i = number of pre-existing ions or ions formed by solvolysis from a molecule

M_i = number of de millimoles of each component

water $_i$ = mass of water of each component in kg

n = number of component of the solution

Figure 3 : OSMOLALITY OF COMPLEXE SOLUTIONS

TABLE 1 : RECURRENCE OF THE OSMOMETER

	Osmolality level		
	Low	Medium	High
n	20	20	20
Min	389	689	1561
Max	410	709	1624
Average	401,25	700,95	1583,30
SD *	4,52	4,96	17,39
C.V.% **	1,1%	0,7%	1,1%

* Standard deviation

** Coefficient of variation

shows directly the result in mosm/kg by applying Raoult's Law. It has just one range of measures from O to 2OOO and its calibration points are set at 5OO and 1OOO. The recurrence studied on standards 4OO, 7OO and 16OO gave variation coefficients nearing 1% in accordance with the performances instructed by the manufacturer (Tab.1).

2-2 Method

2-2-1 Sample

An aliquot (BMPN) is taken for the entire physico-chemical controls before proceeding to the filtration and the conditioning in bags. 2OOµl are measured on this aliquot by means of an automatic pipette, P2OO Gilson and then introduced in a cupule.

2-2-2 Measurement

The measurements are carried out after standardizing the osmometer and going through the control points. The apparatus can freeze BMPN up to osmolalities approximating 18OO ; beyond this, the power of Pelletier's effect is insufficient.

2-2-3 Calculation of the Ideal Osmolality for the BMPN.

The calculation is made by the NUTRIPAR software: a software designed for galenic pharmacy and practical pharmacy by our department. The calculation of the Ideal Osmolality is based on the data of primary solutions, using the formula in Figure 4.

2-3 Plan of the study

2-3-1 Part I

This step aims at creating a relation Em=(iO)f which is simple, reliable and easily applicable when used in daily practice.

$$iO\ (mosm/kg) = \frac{\sum \text{millimoles of primary solutions}}{\sum \text{water of primary solutions}}$$

$$iO\ (mosm/kg) = \frac{\sum_{j=1}^{n} Or_j . v_j}{\sum_{j=1}^{n} v_j . (\rho_j - S_j)}$$

v_j = volume in litre
Or_j = Osmolarity in mosm/l
ρ_j = voluminal mass in kg/l
S_j = mass of dissolved substances per litre in kg/l

Figure 4 : IDEAL OSMOLALITY OF BMPN

Couples of values (iO,Em) were collected for a month so as to determine the parameters of this relation. The function of fundamental loss of least squares is used according to the following formula :

$$S\ (\beta_o, \beta_1, \{Em_i, Oi_i\}) = \sum_{i=1}^{n} e_i^2$$

With :

$$Em_i = \beta_o + \beta_1 . Oi_i + ei$$
$$Ec = Em = \beta_o + \beta_1 . Oi_i$$

The parameters to be determined are β_o and β_1

2-3-2 Part 2

The equation obtained is used to determine an estimated value Ec in function of iO. This value Ec is compared with the corresponding measured value Em, by analysing the deviations (Em - Ec). This enables us to check how good the approximation of the model is.

Table 2 : COUPLES OF VALUES (IO, Em)

N°	IO	Em	N°	IO	Em
01	779	788	45	1122	1042
02	816	831	46	1126	1062
03	831	853	47	1126	1074
04	837	823	48	1130	1105
05	848	835	49	1146	1123
06	936	966	50	1177	1119
07	938	943	51	1197	1191
08	959	975	52	1203	1218
09	963	956	53	1254	1282
10	1006	979	54	1293	1218
11	1006	978	55	1304	1341
12	1007	1028	56	1304	1336
13	1007	1015	57	1317	1237
14	1007	1018	58	1319	1329
15	1016	942	59	1340	1310
16	1016	944	60	1341	1365
17	1021	978	61	1453	1342
18	1021	984	62	1462	1456
19	1022	974	63	1462	1443
20	1022	982	64	1472	1503
21	1024	982	65	1475	1525
22	1024	980	66	1511	1403
23	1030	970	67	1515	1446
24	1059	1054	68	1517	1438
25	1059	1064	69	1517	1450
26	1062	1054	70	1517	1481
27	1062	1058	71	1517	1476
28	1067	1036	72	1587	1462
29	1070	1035	73	1589	1496
30	1073	1020	74	1590	1574
31	1074	1046	75	1632	1579
32	1081	1065	76	1639	1548
33	1081	1056	77	1640	1560
34	1082	1045	78	1655	1642
35	1090	1052	79	1657	1566
36	1092	1056	80	1658	1578
37	1093	1053	81	1661	1582
38	1100	1048	82	1662	1574
39	1100	1052	83	1667	1578
40	1110	1038	84	1667	1572
41	1116	1075	85	1699	1774
42	1116	1098	86	1699	1782
43	1120	1085	87	1699	1782
44	1121	1086			

RESULTS

3-1 Part 1

The 87 couples (iO, Em) shown in table 2 range from 800 mosm/kg. The relation between Em and iO resulted from the observation and settled by the ordinary least squares technique is :

$$Em = 0.964\ iO + 14.506$$

Count n = 87
$r^2 = 0.97$
$r = 0.99$

The adjustment of this straight line to the model therefore enables us to explain 97% of the total variability. Only 3% of the information are lost, which proves that the linear model (Fig.5) is acceptable.

3-2 Part 2

Table 3 shows the deviations (Em - Ec) obtained from 95 consecutive measurements. The graphic analysis (Fig.6) reveals a layout centered around zero whatever the zone measure.The sum of the deviations is equal to 2. The average percentage of the deviations, (Em - Ec) / Ec% is equal to 0.13%

DISCUSSION

4-1 Validity of the model

The pharmaceutical preparations are admitted by the control, if the deviation between the theoretical value and the measured value is less than 10%. In relation to this norm, the mathematical modelisation suggested appears to be sufficiently precise. However the group of measurements used to calculate the least squares line cannot be

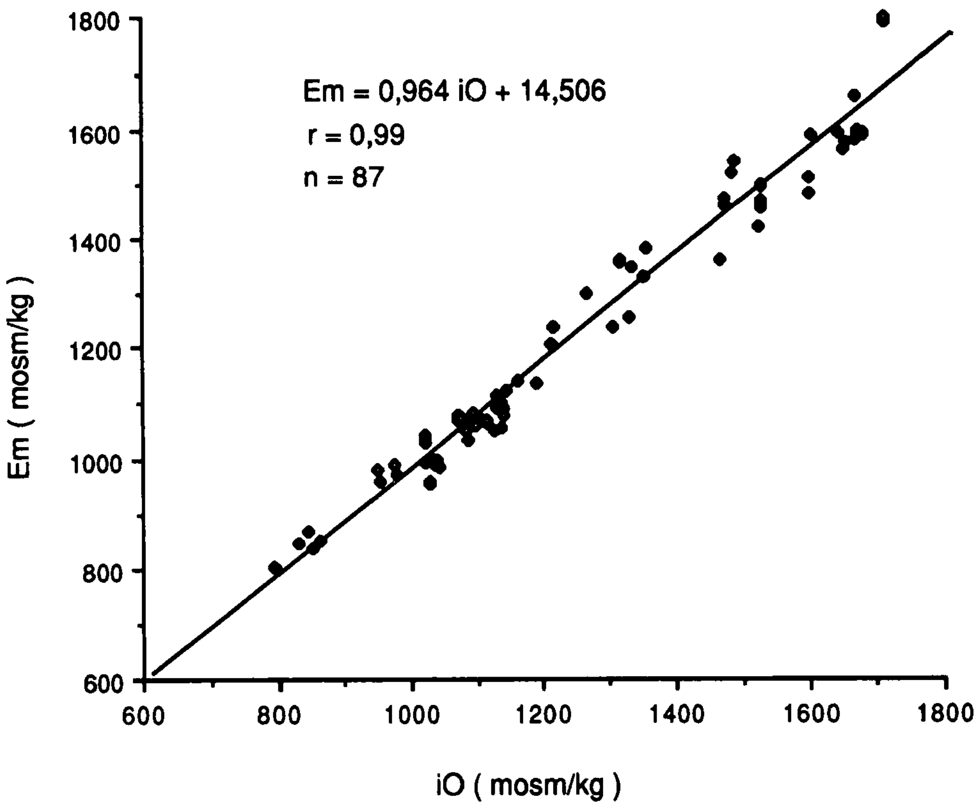

Figure 5 : MODEL Em = f(iO)

TABLE 3 : DEVIATIONS (Em-Ec)

N°	Ec	Em	Em-Ec	(Em-Ec)/Ec%	N°	Ec	Em	Em-Ec	(Em-Ec)/Ec%
01	1135	1044	-91	-7,99	48	879	890	11	1,23
02	1455	1358	-97	-6,65	49	925	937	12	1,24
03	1455	1362	-93	-6,37	50	901	913	12	1,29
04	967	909	-58	-5,99	51	582	590	8	1,32
05	1085	1021	-64	-5,86	52	604	614	10	1,58
06	1057	998	-59	-5,55	53	826	841	15	1,79
07	1007	953	-54	-5,40	54	932	949	17	1,80
08	821	777	-44	-5,40	55	932	949	17	1,80
09	1464	1386	-78	-5,35	56	1204	1227	23	1,90
10	1082	1026	-56	-5,15	57	862	879	17	1,99
11	1464	1390	-74	-5,08	58	1075	1098	23	2,15
12	967	918	-49	-5,06	59	1089	1113	24	2,17
13	1464	1391	-73	-5,01	60	1192	1218	26	2,22
14	967	920	-47	-4,85	61	1321	1351	30	2,29
15	1085	1032	-53	-4,84	62	870	892	22	2,58
16	1284	1223	-61	-4,76	63	1407	1444	37	2,59
17	836	797	-39	-4,65	64	1068	1096	28	2,61
18	758	723	-35	-4,59	65	1618	1660	42	2,62
19	1471	1404	-67	-4,56	66	1589	1632	43	2,72
20	1003	958	-45	-4,45	67	1209	1242	33	2,74
21	1138	1088	-50	-4,36	68	486	500	14	2,90
22	1464	1402	-62	-4,26	69	1010	1042	32	3,14
23	1046	1005	-41	-3,92	70	1366	1409	43	3,15
24	997	959	-38	-3,79	71	932	962	30	3,19
25	967	931	-36	-3,72	72	906	936	30	3,29
26	1085	1046	-39	-3,55	73	1206	1246	40	3,32
27	1588	1534	-54	-3,39	74	836	865	29	3,49
28	1253	1211	-42	-3,37	75	1089	1131	42	3,82
29	1284	1242	-42	-3,28	76	796	828	32	3,98
30	1471	1434	-37	-2,52	77	1345	1401	56	4,18
31	679	663	-16	-2,31	78	1016	1059	43	4,22
32	1253	1225	-28	-2,25	79	1259	1313	54	4,29
33	1429	1410	-19	-1,31	80	1382	1442	60	4,31
34	660	652	-8	-1,27	81	988	1031	43	4,34
35	588	582	-6	-1,03	82	1648	1720	72	4,34
36	802	797	-5	-0,64	83	1206	1259	53	4,39
37	925	920	-5	-0,59	84	1082	1132	50	4,65
38	1334	1327	-7	-0,54	85	1063	1114	51	4,76
39	588	585	-3	-0,52	86	1628	1707	79	4,84
40	768	765	-3	-0,44	87	1357	1424	67	4,91
41	489	487	-2	-0,37	88	1447	1523	76	5,25
42	758	755	-3	-0,36	89	1534	1620	86	5,62
43	1344	1340	-4	-0,29	90	1608	1700	92	5,72
44	646	647	1	0,17	91	1623	1722	99	6,07
45	866	870	4	0,49	92	1327	1409	82	6,22
46	669	675	6	0,89	93	1062	1143	81	7,59
47	691	699	8	1,12	94	1115	1207	92	8,21
							Average	**=**	0,13

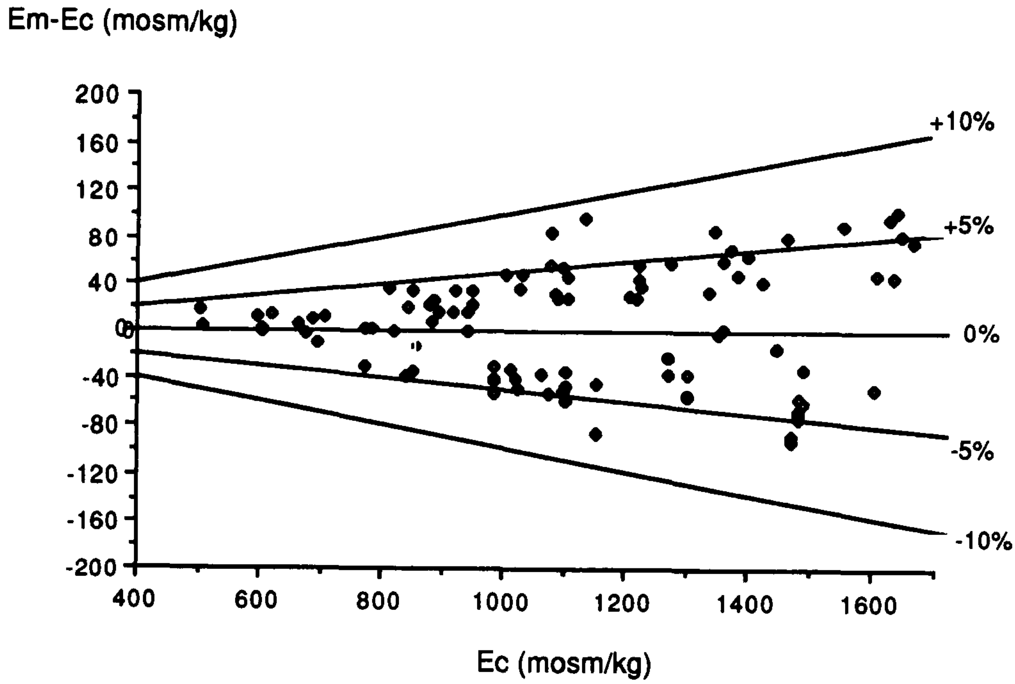

FIGURE 6 : GRAPHIC ANALYSIS OF DEVIATIONS Em-Ec IN FUNCTION OF Ec

considered as a representative sample of all the BMPN. It is only a representative sample of the personalized parenteral nutritions manufactured for children and adults following the instructions of the prescription of E. Heriot Hospital. (This is demonstrated in the second part of the present work).However it is impossible to make a systematic and exhaustive study because of the infinite number of possible formulas for a BMPN and the great variety of primary solutions that can be used. So we advise those who wish to apply this modelisation to calculate their own least squares line.

4-2 Interpretation of the model

If the formula of the model (Em=O.964 iO + 14.5O6) is compared with the *formula of the osmolality of a simple solution* (Em = Φ iO), the slope of the least squares line can be likened to a molal coefficient Φ. In electrolytic solutions, 0 decreases rapidly as the concentration increases. For example, for sodium chloride, 22.38 g/l concentration corresponds to 765.86 osmolality and O.914 molal coefficient. These results reveal that Φ keeps a practically constant value because of the high quantity of amino acids and glucose.

CONCLUSION

This present work demonstrates that it is possible to calculate the osmolality of a binary mixture of parenteral nutrition by using its galenic formula accurately enough to serve as value of reference for the control. Integrating all the calculations in a galenic formulation software means that this control can be done routinely. The systematic control of the osmolality contributes to the safety of the patients.

REFERENCES

L. D. Deardorff, Am J Hosp Pharm., 37, 504 (1980)

L. Gatlin, P. Kulkarni, A. Hussein and P.P. DeLuca, Am J Hosp Pharm., 36,1357 (1979)

B.S.R. Murty, J.N. Kapoor and P.P. DeLuca, Am J Hosp Pharm., 33, 546 (1976)

D.P. Wermeling, R.P. Rapp, P.P. DeLuca, and J.J. Piecoro,Jr, Am J Hosp Pharm., 42, 1739 (1985)

P. Ambroise-Thomas in " Osmolalité ", Journal Officiel de la République Française du 21 Janvier 1989, ?14 (1989)

S. Detolle, S. Lefebvre, O. Corriol, P. Chaumont et M. Hamon., Ann. Pharm. Fr., 46, 7(1988)