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Biomathematical modeling for diluted drugs

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Summary Several workers have proven that succussed ultra high dilution of a drug molecule in water or alcoholic medium, even exceeding Avogadro number, can bring forth noticeable physiological changes of an organism. Homeopathic drugs are prepared by dissolving such drug ingredients in distilled water and then the solution is centesimally diluted serially by ethanol. A mathematical model has been proposed by the present worker, which explains why the drug does not become non-molecular even in ultra-high dilution. This is due to loss of homogeneity in the solution, caused by increase of dielectric constant of the medium during the process of potentization. Facilitated binding of the drug molecules with minute physiologically important protein factors may be the cause of visible physiological alterations.

INTRODUCTION

Generalized technique of 'potentization', applied for the preparation of homeopathic drugs, includes the following steps: the crude drug (collected from plant, animal or mineral origin, or exudates of pathogen-affected tissue), is dissolved in distilled water, mixed with certain amount of absolute ethanol, to prepare the 'Mother tincture'. Small fraction (1 ml) of the tincture taken, again mixed with 99 ml fresh ethanol (centesimal dilution or c) and repeated manual strokes are given at the bottom of the container to prepare 1st potency solution (1c). A small fraction (1 ml) of the 1st potency solution taken and mixed with 99 ml fresh ethanol, repeated manual stroke given at the bottom of the container to prepare 2nd potency solution (2c) and so on. Thus, the original drug is serially diluted by ethanol several times in a repeated and systematic way. Now, suppose one mole pure drug, containing 6.023×10^{23} molecules, has been dissolved in water and added ethanol to make the volume to 100 ml of mother tincture. One millilitre of mother tincture was taken to prepare 100 ml first potency solution (1c), where the number of molecules would be 6.023×10^{21}; after second potentization (2c) would be 6.023×10^{19}; and after twelfth potentization (12c) would be 6.023×10^{-1}, in other words 10^{-24} moles per 100 ml medicine. Hence practically no molecule of the original remedy remains in 100 ml such solution. The materials used to prepare the mother tincture of homeopathic drugs (generally 10 g/100 ml) are much lower than one mole and that becomes non-molecular much earlier than attaining 12c dilution. Surprisingly, several workers have obtained good physiological response, i.e., immunomodulation (1–3), toxic stress protection (4–6) recovery from diseases (7–10); etc., by the pre or post treatment of such type of non-molecular aqueous or alcoholic dilutions. It indicates that living system can act as sensitive tool for the detection of 'vanishingly minute' amount of chemicals (if we do not call them 'non-molecular'). Several workers, including Benveniste (11–14) considered that drugs in non-molecular dilution might bring visible response on living cells; this is called 'pharmacodynamic property of water'. According to these workers this is due to 'memory of water' regarding the chemical nature of drug molecules. Here water molecules acts like 'compact discs' and living cells as 'CD-players'. If successions are made between serial dilutions the impact becomes more visible (1,3).

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The present author intended to explain it by a mathematical model. According to him truly succussed serial dilution cannot bring non-molecular alcoholic or aqueous solution, because the drug molecules, when highly potentized, unduly flows to the next serially diluted solution like gaseous molecules. According to the proposed hypothesis, as mentioned below, such 'memory' is possible primarily due to encapsulation of drug molecule by water molecules, which becomes secondarily covered by ethanol molecules. We shall discuss firstly on aqueous dilution.

ULTRA-HIGH DILUTIONS IN AQUEOUS OR ALCOHOLIC MEDIUM

We know that water has a high dielectric constant (=80), so it widely separates charges of a solute, antigen, electrolyte or drug molecule in a solution.Water molecules remain sparsely associated with the surface of positive and negative charges of the drug molecules by hydrogen bonds or ion dipole interaction ('bared Capsule'). Centesimal dilution gradually increases number of solvent molecules (Fig. 1) per solute molecule. Succussion is done by repeated manual stroke at the bottom of the container and it is comparable to sonication, which is able to rearrange the solvent molecules according to their best thermodynamically possible orientation. Centesimal dilution initially cannot affect homogeneity of a solution and the solute behaves like ideal gaseous molecules. After several repetition of the process water molecules rearrange themselves more closely covering the surface of charges of the solute ('rough capsule'), formation and dissociation of hydrogen bonds become quicker, so that van der Waals force (which is a result of both permanent dipoles and circulation of electrons) between adjacent water molecules

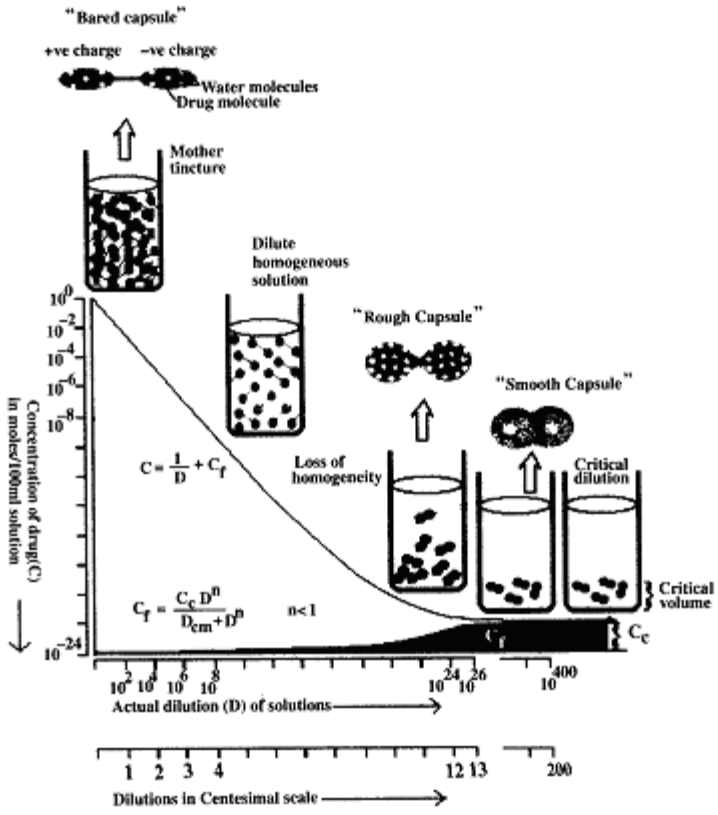

Fig. 1 Attainment of critical concentration of a drug by succussion and centesimal dilution.

increases enormously. Van der Waals forces (F) are inversely proportional to the seventh power of the distance (d) between the dipoles: $F \propto 1/d^7$. Thus the attraction is a very weak force in low dilution and is significant only in ultra high dilution, when two dipoles (water molecules) are very near to one another. Enormous increase of van der Waals force in ultra high dilution, as mentioned above, creates a 'screening effect' on the opposite charges of the solute, they come into more and more close proximity, in spite of high dielectric constant of the solvent, and become more strongly encapsulated by water molecules. Homogeneity of the solution is lost and a definite density gradient becomes established. Gradually, after repetition of this process, the encapsulated solute molecules become very negligible in number, but more strongly protected by water capsule in the form of a smooth hydration sheath ('smooth capsule'), because the attraction between like-atoms (H–H, O–O) or unlike-atoms (H–O) of two adjacent water molecules increases as they come closer, until they are separated by van der Waals contact distance (sum of van der Waals radii of those atoms). In such condition drug molecules can no more be separated from the hydration sheath by any physical process, but they can hardly occupy the total volume (100 ml) of the solution, and become more and more restricted at the bottom of the container, where they move very fast like gaseous molecules within a small space of volume. When the volume becomes restricted within 1 ml of such type of solution, one would be able to lift it by a dropper and add it to 99 ml fresh distilled water to prepare the next centesimal dilution; the concentration of the second solution would remain unchanged. Then we shall call the transferred volume as *critical volume*; here it equals to 1 ml, and the fixed concentration should be termed as *critical concentration* (C_c). Practically there would be no way to make the next serial dilutions without transferring majority of the critical volume, because the encapsulated molecules would move very fast like gaseous molecules towards the fluvial (flowing) part of the solution during the transfer process. The concentration of such encapsulated molecules, which flows unduly with serial dilution, should be termed as *fluvial concentration* (C_f). Mathematically, if C be the concentration of a drug, expressed as number of moles per 100 ml solution, against succussed dilution D then

$$C \propto 1/D \quad \text{or } C = k/D.$$

Initially, if a solution containing 1 mole drug /100 ml is centesimally diluted (actually 100 times), the number of moles would be 10^{-2}. If the latter were again centesimally diluted serially by 10^4, 10^6, and 10^8 times, the number of moles would be 10^{-4}, 10^{-6}, and 10^{-8} respectively. Hence the value of k is equal to 1 or $C = 1/D$. Thus concentration of drug would fall with increase of succussed dilution, but would not reach 10^{-24} (non-molecular state) due to subsequent increase of fluvial concentration (C_f), as mentioned above, that aberrantly flows to the next serial dilution, Hence

$$C = \frac{1}{D} + C_f. \qquad [1]$$

Initially there would be no significant effect of dilution on van der Waals force, because it is inversely proportional to the seventh power of the distance between the water molecules that are wide apart in a low diluted solution, but when the solution is of ultra high dilution, succussion can bring water molecules into close approximation around the surface of drug molecules and fluvial transfer of drug molecules becomes significant one. So, increase of C_f with dilution becomes sigmoid, $C_f \propto D^n$, here $n < 1$ (where n is an indication of potentization efficiency) and it seems to be asymptotic to the critical concentration C_c, when all the remnant molecules become fluvial. It is mathematically very difficult and useless also to determine the exact dilution (or *critical dilution*, D_c) at which all the drug molecules that still remain after endless serial dilution, become fluvial, or C_c equals to C_f. So we would define an easier term, the *median critical dilution*, D_{cm} as follows:

$$C_f = \frac{C_c D^n}{D_{cm} + D^n}. \qquad [2]$$

When $C_f = C_c/2$ $D^n = D_{cm}$. Hence median critical dilution D_{cm} can be defined as a function of dilution, at which half of the maximal possible number of drug molecules, due to succussion and centesimal dilution, become restricted within a critical volume (= 1 ml). Value of D_{cm} for the same drug might vary widely in different solvents, due to wide difference in dielectric constants. Polar solvents of low dielectric constant, e.g., ethanol (=24), if added gradually to such a solution, may decrease D_{cm} due to more easy reestablishment of attraction force between opposite charges of drug molecules resulting an increase the 'screening effect', as mentioned earlier. Due to special orientation of ethanol molecules during succussion (comparable to sonication) the water capsulated drug molecules get secondarily encapsulated by ethanol, like drug-loaded liposomes, and become easily concentrated at the bottom layer of the solution (15). That confers ethanol to be more efficient medium for potentization than that of distilled water, so that value of n would increase, and fluvial concentration in relation to dilution in alcoholic medium would be more hyperbolic. In such case ethanol would also be able to trap more drug-loaded water molecules, so that C_c would increase accordingly. Hence, so-called 'non-molecular' homeopathic drugs might not be truly

non-molecular, though non-detectable by spectrophotometry.

EFFECT OF ULTRA-HIGH DILUTION DRUGS ON LIVING CELLS

Though several workers have studied the effect of non-molecular dilution, a very few of them (1,14,15) have endeavored to solve the fallacy of non-molecularity. The minute enzymes, transcription factors, hormone-receptor, interleukin-receptors, etc. are physiologically most important protein factors or 'hot-spots', being very few in quantity, can activate several molecules of subordinate enzymes and the incoming signal that comes from a picogram level endogenous molecules becomes enormously amplified. Strongly 'encapsulated' drug molecule being protected from detoxification and immune systems of the body, achieves great penetration power (15) into each and every cells suspended into the body fluid, due to high velocity. If the drug becomes ligand-inhibitor of such a minute protein factor, may bind the same more easily, and attains thermodynamically more stable form. Such protein factors may also act as rate limiting factors for diseased individuals. When they bind any drug molecule the inhibition would be much pronounced and the signal would reach to the gene in much amplified form. For healthy individuals there might be a little scope for the rectification of the rate of protein synthesis by minute dose drugs (15), because most of them are predetermined according to their necessity. If the animal becomes weak, or immunodepressed (1–3) expression of a gene may be triggered or might be rectified in course. Hence the diseased individuals would act as a more sensitive tool to prove the proposed model.

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REFERENCES

1. Bastide M., Daurat V., Doucet-Jaboeuf M., Pelegrin A., Dorfman P. Immuno-modulatory activity of very low doses of thymulin in mice. *Int J Immunother* 1987; **3**: 191–200.
2. Youbicier-Simo B. J., Boudard F., Mekaouche M., Bastide M., Baylé J. D. Effects of embryonic bursectomy and *in ovo* administration of highly diluted bursin on adrenocorticotropic and immune response of chickens. *Int J Immunother* 1993; **9**: 169–180.
3. Guennoun M, Boudard F, Cabaner C, Robbe Y, Dubois JB, Bastide M. Radioprotection and immune system regeneration of irradiated mice by using high dilution treatment. *Alternative Therapies*, January, San Diego, USA, 1996, p. 64.
4. Cazin J. C., Cazin M., Gaborit J. L., Chaoui A., Boiron J., Belon P., Cherruault Y., Papayanotou C. A study of the effect of decimal and centesimal dilutions of arsenic on the retention and mobilization of arsenic in the rat. *Hum Toxicol* 1987; **6**: 315–320.
5. Begum R., Koshy R., Sengupta A. Effect of homeopathic drugs plumbum and opium on experimentally induced lead toxicity in rats. *Indian J Exp Biol* 1994; **32**(3): 192–195.
6. Fisher P., House I., Belon P., Turner P. The influence of the homeopathic remedy Plumbum met on the excretion kinetics of lead in rats. *Hum Toxicol* 1987; **6**: 321–324.
7. Kurz C., Nagele F., Zorzi M., Karras H., Einzelsberger H. Bewirkt Homeopathie eine Verbesserung der Reizblasensymptomatik. *Gynaekol geburtshilfiche Rundsch* 1993; **33**: 330–331.
8. Sudan B. J. L. Abrogation of facial seborrhoeic dermatitis with homeopathic high dilution of tobacco: a new visible model for Benveniste's theory of memory of water. *Med Hypotheses* 1993; **41**: 440–444.
9. Lüdtke R., Wisenaurer M. A meta-analysis of homeopathic treatment of pollinosis with *Galphimia gluca*. *Wien Med Wochenschr* 1997; **147**(14): 323–327 [In German].
10. Oberbaum M., Markovits R., Weissman Z., Klinkevits A., Bentwich Z. Wound healing by homeopathic silica dilutions in mice. *Harefuah* 1992; **123**: 79–82.
11. Davenas E., Beauvais F., Amara J., Oberbaum M., Robinzon B., Miadonna A., Tedeschi A., Pomeranz B., Fortner P., Belon P., Sainte-Laudy J., Poitevin B., Benveniste J. Human basophil degeneration triggered by very dilute antiserum against IgE. *Nature* 1988; **333**: 816–818.
12. Draaisma D. Voorbij het getal van Avogadro: de Benveniste-affaire. *Kennis en Methoden* 1989; **13**: 84–107.
13. Delbancut A, Barouillet MP, Camber J. Evidence and mechanistic approach of the protective effects of heavy metal high dilutions in rodents and renal cell cultures. Communications presented at the 7th GIRI Meeting, November, 1993, Montpellier, France, and at the 8th GIRI Meeting, December, 1994, Jerusalem, Israel.
14. Endler P. C., Pongratz W., Smith C. W., Schulte J., Senekowitsch F., Citro M. Non molecular information transfer from thyroxine to frogs. In: M. Bastide (ed). *Signal and Images*. Dordrecht: Kluwer Academic Publisher, 1997: 149–161.
15. Chattopadhyay S. Proposition of a new system of medicine based on tolerance principle. *Med Hypotheses* 2002; **59**(2): 191–203.