



A OVERVIEW ON TASTE MASKED ORAL DISINTEGRATING TABLETS FOR ANTI- VERTIGO DRUG

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Abstract: Drug Delivery Systems (DDS) are a strategic tool for expanding markets/indications, extending product life cycles and generating opportunities. DDS make a significant contribution to global pharmaceutical sales through market segmentation, and are moving rapidly. Drug delivery systems are becoming increasingly sophisticated as pharmaceutical scientists acquire a better understanding of the physicochemical and biochemical parameters pertinent to their performance. Despite of tremendous advancements in drug delivery, the oral route remains the perfect route for the administration of therapeutic agents because of low cost of therapy, ease of administration, accurate dosage, self - medication, pain avoidance, versatility, leading to high levels of patient compliance

Index Terms - Drug Delivery Systems, low cost of therapy, ease of administration, accurate dosage, self - medication, pain avoidance, versatility

I. INTRODUCTION

Drug Delivery Systems (DDS) are a strategic tool for expanding markets/indications, extending product life cycles and generating opportunities. DDS make a significant contribution to global pharmaceutical sales through market segmentation, and are moving rapidly. Drug delivery systems are becoming increasingly sophisticated as pharmaceutical scientists acquire a better understanding of the physicochemical and biochemical parameters pertinent to their performance¹.

Despite of tremendous advancements in drug delivery, the oral route remains the perfect route for the administration of therapeutic agents because of low cost of therapy, ease of administration, accurate dosage, self - medication, pain avoidance, versatility, leading to high levels of patient compliance. Tablets and capsules are the most popular dosage forms. But one important drawback of such dosage forms is 'Dysphagia' or difficulty in swallowing. This is seen to afflict nearly 35% of the general population. This disorder is also associated with a number of conditions like:

1. Parkinsonism
2. Motion sickness
3. Unconsciousness
4. Elderly patients
5. Children
6. Mentally disabled persons
7. Unavailability of water

Improved patient compliance has achieved enormous demand. Consequently demand for their technologies is also increasing many folds. To develop a chemical entity, a lot of money, hard work and time are required. So focus is rather being laid on the development of new drug delivery systems for already existing drugs, with enhanced efficacy and bioavailability, thus reducing the dose and dosing frequency to minimize the side effects. It is always the aim of a scientist or a dosage form designer to enhance the safety of a drug molecule while maintaining its therapeutic efficacy. Recent advances in Novel Drug Delivery Systems (NDDS) aim for the same by formulating a dosage form, convenient to be administered so as to achieve better patient compliance. Pharmaceutical technologists have put in their best efforts to develop a Fast Dissolving Drug Delivery System, i.e DispersibleTablet¹.

1.2 Orally Disintegrated Tablet (ODT)

It is a tablet that disintegrates and dissolves rapidly in the saliva, within a few seconds without the need of drinking water or chewing. A Dispersible tablet usually dissolves in the oral cavity within 15 s to 3 min. Most of the ODTs include certain super disintegrants and taste masking agents.

1.3 Ideal properties of ODT

1. A Orally Disintegrated Tablet should
 - a. Not require water or other liquid to swallow.
 - b. Easily dissolve or disintegrate in saliva within a few seconds.
 - c. Have a pleasing taste.
 - d. Leave negligible or no residue in the mouth when administered.
2. Be portable and easy to transport.
3. Be able to be manufactured in a simple conventional manner within low cost.
4. Be less sensitive to environmental conditions like temperature, humidity etc¹.

1.4 Advantages of ODT

1. No need of water to swallow the tablet.
2. Can be easily administered to pediatric, elderly and mentally disabled patients.
3. Accurate dosing as compared to liquids.
4. Dissolution and absorption of drug is fast, offering rapid onset of action.
5. Bioavailability of drugs is increased as some drugs are absorbed from mouth, pharynx and esophagus through saliva passing down into the stomach.
6. Advantageous over liquid medication in terms of administration as well as transportation.
7. First pass metabolism is reduced, thus offering improved bioavailability and thus reduced dose and side effects.
8. Free of risk of suffocation due to physical obstruction when swallowed, thus offering improved safety.
9. Suitable for sustained/controlled release actives¹.

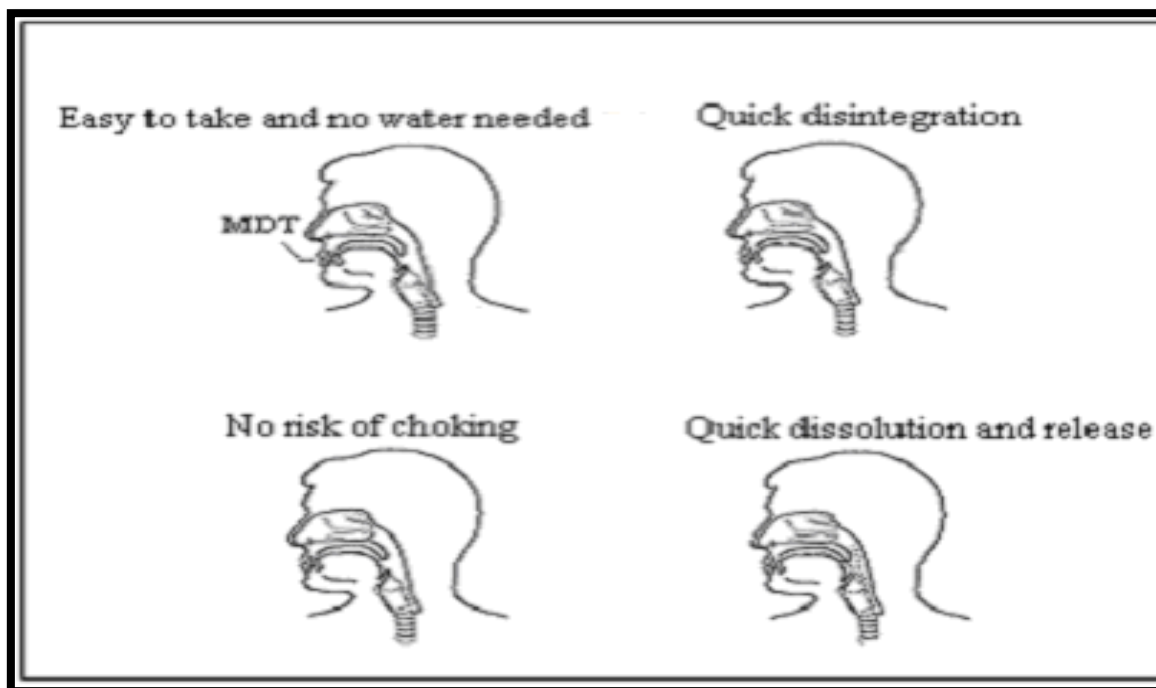


Fig. 1: Advantages of ODT

1.5 Mechanism of action of disintegrants

The tablet breaks to primary particles by one or more of the mechanisms listed below: -

- By capillary action
- By swelling
- Because of heat of wetting
- Due to release of gases
- By enzymatic action
- Due to disintegrating particle/particle repulsive forces
- Due to deformation

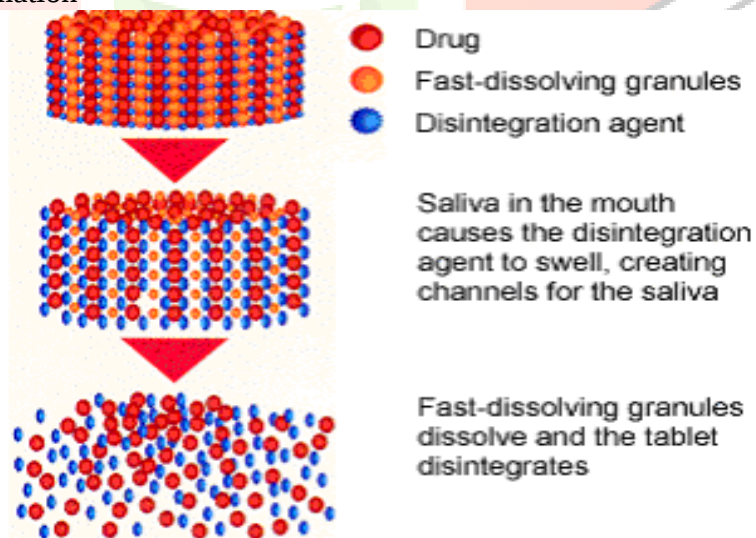


Fig. 2: Mechanism of Action of Superdisintegrants

1.6 Criteria for Fast dissolving Drug Delivery System²:

- The tablets should not require water to swallow, but it should dissolve or disintegrate in the mouth in matter of seconds.
- Be compatible with taste masking.
- Be portable with taste masking.
- Have a pleasant mouth feel.
- Leave minimum or no residue in the mouth after oral administration.
- Exhibit low sensitive to environmental condition as Temperature and humidity.
- Allow the manufacture of the tablet using conventional processing and packaging equipments at low cost.

1.7 Salient Feature of Fast Dissolving Drug Delivery System²:

- Ease of Administration to the patient who cannot swallow, such as the elderly, stroke victims, bedridden patients, patient affected by renal failure and patient who refuse to swallow such as pediatric, geriatric & psychiatric patients.
- No need of water to swallow the dosage form, which is highly convenient feature for patients who are traveling and do not have immediate access to water.
- Rapid dissolution and absorption of the drug, which will produce quick onset of action.
- Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases bioavailability of drug is increased.
- Pre gastric absorption can result in improved bioavailability and as a result of reduced Dosage; improve clinical performance through a reduction of unwanted effects.
- Good mouth feel property helps to change the perception of medication as bitter pill particularly in pediatric patient.
- The risk of choking or suffocation during oral administration of conventional formulation due to physical obstruction is avoided, thus providing improved safety.
- New business opportunity like product differentiation, product promotion, patent extensions and life cycle management.
- Beneficial in cases such as motion sickness, sudden episodes of allergic attack or coughing, where an ultra rapid onset of action required.
- An increased bioavailability, particularly in cases of insoluble and hydrophobic drugs, due to rapid disintegration and dissolution of these tablets.
- Stability for longer duration of time, since the drug remains in solid dosage form till it is consumed. So, it combines advantage of solid dosage form in terms of stability and liquid dosage form in terms of bioavailability.

1.8 Limitations of Dispersible Tablets²:

The tablets usually have insufficient mechanical strength. Hence, careful handling is required. The tablets may leave unpleasant taste and/or grittiness in mouth if not formulated properly.

1.9 Newer manufacturing technologies used now days for ODT's³:

Some of the new advanced technologies which are commonly being used in last few decades are summarized as:-

- a) Freeze drying/Lyophilization
- b) Molding
- c) Direct Compression
- d) Cotton Candy Process
- e) Spray Drying
- f) Sublimation
- g) Mass Extrusion
- h) Nanonization
- i) Fast Dissolving Films

a) Freeze drying or lyophilization: -

It is one of the first generation techniques for preparing ODT, in which sublimation of water takes place from the product after freezing. The formulations show enhanced dissolution characteristics due to the appearance of glossy amorphous structure to bulking agents and sometimes to drug. The ideal drug characteristics for this process are relative water insolubility with fine particle size and good aqueous stability in suspensions. Primary problems associated with water-soluble drugs are formation of eutectic mixture, because of freezing point depression and formation of glassy solid on freezing, which might collapse on sublimation. The addition of mannitol or crystal forming materials induces crystallinity and imparts rigidity to amorphous material. The advantage of using freeze-drying process is that pharmaceutical substances can be processed at non elevated temperature, thereby eliminating adverse thermal effects. High cost of equipment and processing limits the use of this process. Other disadvantages include lack of resistance necessary for standard blister packs of the final dosage forms³.

b) Tablet Molding: -

There are two types of molding process i.e. solvent method and heat method. Solvent method involves moistening the powder blend with a hydro-alcoholic solvent followed by compression at low pressures in molded plates to form a wetted mass (compression molding). Air-drying is done to remove the solvent. The tablets manufactured so formed are less compact than compressed tablets and possess a porous structure that hastens dissolution. In the heat molding process a suspension is prepared that contains a drug, agar and sugar (e.g. mannitol or lactose). This suspension is poured in the blister packaging wells, and then agar is solidified at the room temperature to form a jelly and dried at 30°C under vacuum. The main concern about these molded tablets is their mechanical strength, which can be achieved by using binding agents. The spray congealing of a molten mixture of hydrogenated cottonseed oil, sodium carbonate, lecithin, polyethylene glycol and an active ingredient into a lactose based tablet triturate form was used to prepare the taste masked drug particles. As compared to the lyophilization technique, tablets produced by the molding technique are easier to scale up for industrial scale manufacturing³.

c) Direct Compression:-

Direct compression represents the simplest and most cost effective tablet manufacturing technique. ODT can be prepared by using this technique because of the availability of improved excipients especially super-disintegrants and sugar based excipients.

(a) Super-disintegrants: - The rate of disintegration gets affected by the addition of superdisintegrants and hence the dissolution. Other ingredients like water-soluble excipients and effervescent agents also increase the disintegration.

(b) Sugar based excipients: - The sugar based excipients which are commonly used are especially bulking agents (like dextrose, fructose, lactitol, maltitol, maltose, mannitol, sorbitol, starch hydrolysate, polydextrose and xylitol) which display high aqueous solubility and sweetness, and hence impart taste masking property and provide pleasing mouth feel. Mizumoto et al classified sugar-based excipients into two types on the basis of molding and dissolution rate:

Type 1 saccharides (lactose and mannitol) exhibit low mouldability but high dissolution rate.

Type 2 saccharides (maltose and maltitol) exhibit high mouldability but low dissolution rate³.

d) Cotton Candy Process: -

The FLASHDOSE® is a MDDDS manufactured using Shearform™ technology in association with Ceform TI™ technology to eliminate the bitter taste of the medicament. A matrix known as 'floss', with a combination of excipients, either alone or with drugs is prepared by using shear form technology. Like cotton-candy fibers floss is fibrous material made of saccharides such as sucrose, dextrose, lactose and fructose at temperatures ranging between 180–266 °F. However, other polysaccharides such as polymaltodextrins and poly-dextrose can be transformed into fibers at 30–40% lower temperature than sucrose. Due to this modification thermo labile drugs can be safely incorporated into the formulation. This process results in a highly porous product and offer very pleasant mouth feel due to fast solubilization of sugars in presence of saliva. The manufacturing process can be divided into four steps as detailed below:

(a) Floss blend: - The floss mix is prepared by blending the 80% sucrose in combination with mannitol/dextrose and 1% surfactant. The surfactant maintains the structural integrity of the floss fibers by acting as crystallization enhancer. This process helps in retaining the dispersed drug in the matrix, thereby minimizes the migration out of the mixture.

(b) Floss processing: - The floss formation machine uses flash heat and flash flow processes to produce matrix from the carrier material. The machine is similar to that used in 'cotton-candy' formation which consists of a spinning head and heating elements. In the flash heat process, the heat induces an internal flow condition of the carrier material. This is followed by its exit through the spinning head (2000–3600 rpm) that flings the floss under centrifugal force and draws into long and thin floss fibers, which are usually amorphous in nature.

(c) Floss chopping and conditioning: - In this step fibers are converted into smaller particles in a high shear mixer granulator. The partial crystallization is done by spraying ethanol (1%) onto the floss and subsequently evaporated it to impart improved flow and cohesive properties to the floss. This is called Conditioning.

(d) Blending and compression: - Finally, the chopped and conditioned floss fibers are blended with the drug and other excipients and compressed into tablets. Exposure of the dosage forms to elevated temperature and humidity conditions (40 °C and 85% RH for 15min) improves the mechanical strength of tablets due to expected crystallization of floss material that result in binding and bridging, to improve the structural strength of the dosage form³.

e) Sprays-Drying: -

Allen et al., have used spray-drying for the production of ODT. The formulations contained hydrolyzed and non hydrolyzed gelatin as a supporting agent for the matrix, mannitol as a bulking agent and sodium starch glycolate or croscarmellose as a disintegrant. By adding an acid (e.g., citric acid) or an alkali (e.g., sodium bicarbonate) disintegration and dissolution were further enhanced. The porous powder was obtained by spray drying the above suspension which was compressed into tablets. Tablets manufactured by this method shows disintegration time < 20 sec in an aqueous medium³.

f) Sublimation: -

To produce ODT with high porosity, sublimation is the technique which has been used successfully. When volatile ingredients are compressed along with other excipients into tablets, a porous matrix is formed which are finally subjected to a process of sublimation. For this purpose inert solid ingredients with high volatility (e.g., ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, hexamethylene tetramine, naphthalene, urea and urethane) have been used. Solvents such as cyclohexane and benzene were also suggested for generating the porosity in the matrix³.

g) Mass-Extrusion:-

This technology involves softening of the active blend using the solvent mixture of water soluble polyethylene glycol and methanol. This softened mass is extruded through the extruder or syringe and a cylindrical shaped extrude is obtained which are finally cut into even segments using heated blade to form tablets. Granules of bitter drugs can be coated using this method to mask their taste³.

h) Nanonization: -

A recently developed Nanomelt technology involves reduction in the particle size of drug to nano size by wet-milling technique. Surface adsorption of the nano crystals of the drug is done on selected stabilizers for stabilizing them against agglomeration, which are then incorporated into ODT. This technique is mainly advantageous for poor water soluble drugs and also for a wide range of doses (up to 200 mg of drug per unit)³.

i) Fast Dissolving Films: -

It is a newer developing front in MDDDS that provides a very convenient means of taking medications and supplements. In this technique, water soluble film forming polymer (pullulan, CMC, HPMC, HEC, HPC, PVP, PVA etc.), drug and other taste masking ingredients are dissolved in non-aqueous solvent to prepare non-aqueous solution, which on evaporation of solvent forms a film. Resin adsorbate or coated micro particles of the drug can be incorporated into the film if the drug is bitter. this film when placed in mouth melts or dissolves rapidly and release the drug in solution or suspension form. This system forms the thin films of size less than 2 X 2 inches which dissolves within 5 sec with instant drug delivery and flavored taste³.

1.11 Preformulation studies fast dissolving tablet⁴

Preformulation study relates to pharmaceutical and analytical investigation carried out proceeding and supporting formulation development efforts of the dosage form of the drug substance. Preformulation yields basic knowledge necessary to develop suitable formulation for the toxicological use. It gives information needed to define the nature of the drug substance and provide frame work for the drug combination with pharmaceutical excipients in the dosage form. Hence, the following Preformulation studies were performed on the obtained sample of drug.

a) Bulk density (Db)

It is the ratio of total mass of powder to the bulk volume of powder. It is expressed in g/ml. This was determined by pouring an accurately weighed quantity of blend into a graduated cylinder and then the volume and weight was measured.

$$D_b = M / V_b$$

Where, Bulk density = D_b ,

Weight of powder = M ,

Volume of packing = V_b .

b) Tapped density (ODT)

It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times and the tapped volume was noted if the difference between these two volumes is less than 2%. If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2 % (in a bulk density apparatus). It is expressed in g/mL and is given by

$$ODT = M / V_t$$

Where, M is the mass of powder,

V_t is the tapped volume of the powder.

c) Compressibility

The compressibility index (Carr's Index) was determined by using following equation,

$$\text{Carr's Index (\%)} = [(ODT - D_b) \times 100] / ODT$$

Where,

ODT is the tapped density of the powder,

D_b is the bulk density of the powder.

Table 1: Relationship between % compressibility and flow ability

% Compressibility	Flow ability
5-12	Excellent
12-16	Good
18-21	Fair passable
23-35	Poor
33-38	Very poor
< 40	Very very poor

d) Angle of repose (θ)

The friction forces in a loose powder can be measured by the angle of repose (θ). It is an indicative of the flow properties of the powder. It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane. The angle of repose was determined by the funnel method. The accurately weighed powder was taken in a funnel. The height of a funnel was adjusted in such a way that its tip just touches the apex of the heap of the powder. The powder was allowed to flow through funnel freely onto the surface. The diameter of the powder heap was measured and angle of repose was calculated using following equation,

$$\tan(\theta) = h/r$$

$$\theta = \tan^{-1}(h/r)$$

Where, θ is the angle of repose,
 h is the height in cm,
 r is the radius in cm.

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of powder formed. Care was taken to see that the powder particles slip and roll over each other through the sides of the funnel. Relationship between angle of repose and powder flow property.

Table 2: Angle of repose as an indication of powder flow properties

S. No.	Angle of repose (°)	Type of flow
1	< 20	Excellent
2	20-30	Good
3	30-34	Passable
4	> 34	Very poor

e) Hausner ratio

Hausner ratio is an indirect index of ease of powder flow. Hausner ratio is the ratio of tapped density to bulk density, i.e.,

$$\text{Hausner ratio} = \text{ODT} / D_b$$

Where, ODT is the tapped density,
 D_b is the bulk density.

Powder with Hausner ratio less than 1.18, 1.19, 1.25, 1.3- 1.5 and greater than 1.5 indicate excellent, good, passable, and very poor, respectively.

f) Porosity

Percent relative porosity (ϵ) was obtained using the relationship between apparent density (ρ_{app}) and true density (ρ_{true}) which is calculated by following formula.

$$\epsilon = (1 - \rho_{app} / \rho_{true}) \times 100$$

g) Drug excipient compatibility study

This study was carried out to detect any changes on chemical constitution of the drug after combined it with the excipients. Compatibility of the drug with excipients was determined by FT-IR spectral analysis.

1.10 Evaluation of Dispersible Tablets⁵

a) Measurement of Tablet Tensile Strength:-

The tablet tensile strength is the force required to break a tablet by compressing it in the radial direction and is measured using a tablet hardness tester. For measuring the hardness of the tablets, the plunger of the hardness tester is driven down at a speed of 20 mm/min. Tensile strength for crushing (T) is calculated using equation I:

$$\text{Eq. I. } T = 2F / \pi ODT$$

Where F is the crushing load, and d and t denote the diameter and thickness of the tablet, respectively. Though, this is a widely used and accepted method for hardness testing, it is not applicable to very delicate tablets prepared by lyophilization technique wherein the liquid suspension of drug and excipients is freeze dried in the blister pocket and the dried tablets are finally sealed in the blister. Special aluminum (alu) blisters with peel off blister covers are used as packaging material for these tablets. Flashdose tablets prepared by cotton candy process are also poor candidates for this test. This test is best suited for tablets prepared by direct compression and moulding methods. However, the tensile strength of these tablets is always kept low which needs to be compromised to keep the disintegration time as minimum as possible⁵.

a) Friability

The pharmacopoeial limit of friability test for a tablet is not more than 1% using tablet friability apparatus, carried out at 25 rpm for 4 min (100 rotations). However, it becomes a great challenge for a formulator to achieve friability within this limit for ODT product keeping hardness at its lowest possible level in order to achieve a minimum possible disintegration time. This test is again not applicable for lyophilized and flashdose tablets, but is always recommended for tablets prepared by direct compression and moulding

techniques to ensure that they have enough mechanical strength to withstand the abrasion during shipping and shelf life⁵.

b) Moisture Uptake Study

ODT usually contain high concentration of hydrophilic excipients with the minimum possible hardness which together contribute to their increased susceptibility to moisture uptake. In order to maintain their physical integrity and surface texture, special attention is required during the storage and packaging of these dosage forms. Therefore, moisture uptake studies are strongly recommended for ODT. The test can be carried out by keeping ten tablets along with calcium chloride in a desiccator maintained at 37 °C for 24 hrs to ensure complete drying of the tablets. The tablets are then weighed and exposed to 75% RH, at room temperature for 2 weeks. The required humidity can be achieved by keeping saturated sodium chloride solution in the dessicator for 24 hrs. The tablets are reweighed and the percentage increase in weight is recorded. If the moisture uptake tendency of a product is high, it requires special dehumidified area for manufacturing and packing. The materials with high moisture resistant properties should be used for packaging for e.g. alu strip pack, alu-alu blister or polyethylene sealing on blister. The use of appropriate quantity of desiccant in HDPE bottle packs with minimum head space is highly recommended to ensure stability of the product during its shelf life⁵.

c) Measurement of Tablet Porosity

The mercury penetration porosimeter can be used to measure the tablet porosity which is a relative assessment of the degree of water penetration in the formulation, responsible for its fast disintegration. This instrument is based on the capillary rise phenomenon wherein an excess pressure is required to cause a non-wetting liquid to climb up a narrow capillary. The pressure difference across the interface is given by the Washburn equation II, where the pressure drop is inversely related to the pore size (perpendicular radius).

$$\text{Eq. II. } \Delta P = -(2\gamma/r) \cos \theta$$

where γ is the surface tension of the liquid, r is the perpendicular radius and θ is the angle of contact between the liquid and the capillary walls.

Pore radius is calculated from eq II using experimental data obtained in the form of P . In this test, the contact angle between mercury and the tablet is kept at 140° and the surface tension at the interface of mercury

and the tablet is 0.486 N/m. Pore sizes in the range of 0.06–360 μm , can be efficiently measured by this technique. Otherwise, the tablet porosity (ε) can also be calculated using equation III:

$$\text{Eq. III. } \varepsilon = 1 - m / (\rho_t V)$$

Where ρ_t is the true density, and m and V are the weight and volume of the tablet, respectively.

Tablets prepared by spray drying, lyophilization and cotton candy process generally possess high porosity and therefore, have extremely low disintegration time⁵.

d) Wetting Time and Water Absorption Ratio

A study on wetting time and water absorption ratio reported the use of a piece of double folded tissue paper placed in a petridish containing 6 ml of water. One tablet was placed on this paper and the time for complete wetting of tablet was noted as wetting time. The wetted tablet was then weighed and the water absorption ratio, R , was determined according to equation IV:

$$\text{Eq. IV. } R = 100 (W_a - W_b) / W_b$$

Where W_b and W_a are the weights of tablet before and after water absorption, respectively⁵.

e) Fineness of Dispersion

This is a qualitative test specified by EP for dispersible tablets. We recommend performing this test on tablets which are not truly mouth dissolving, but are fast oral disintegrating tablets (OODTs). It is an assessment of the grittiness which arises due to disintegration of the tablet into coarse particles. The test is performed by placing two tablets in 100 ml water and stirring it gently, till the tablets get completely disintegrated. The formulation is considered to form a smooth dispersion if the complete dispersion passes through a sieve screen with a nominal mesh aperture of 710 μm without leaving any residue on the mesh⁵.

f) Disintegration Time

At present, the disintegration time of ODT is measured using the disintegration test for conventional tablets that is described in the Pharmacopoeias. EP has set the limit of 3 mins for disintegration time of ODT using conventional disintegration apparatus. However, no special apparatus is mentioned in the pharmacopoeias for disintegration test of ODT and the conventional method available seems to be inappropriate for ODT. This is because of the extreme operating conditions in the disintegration apparatus which fails to provide a significant discrimination among the rapidly disintegrating tablets. Furthermore, the conventional test employs a relatively huge volume of test solution (900 ml) compared to the volume of saliva in human buccal cavity, which is less than 6 ml. Therefore, the results obtained from the conventional disintegration test do not reflect the actual disintegration rate in the human mouth which usually ranges from 5–30 secs. To overcome these issues, several new methods have been proposed, which are reviewed here⁵.

Disintegration Test using Modified Dissolution Apparatus

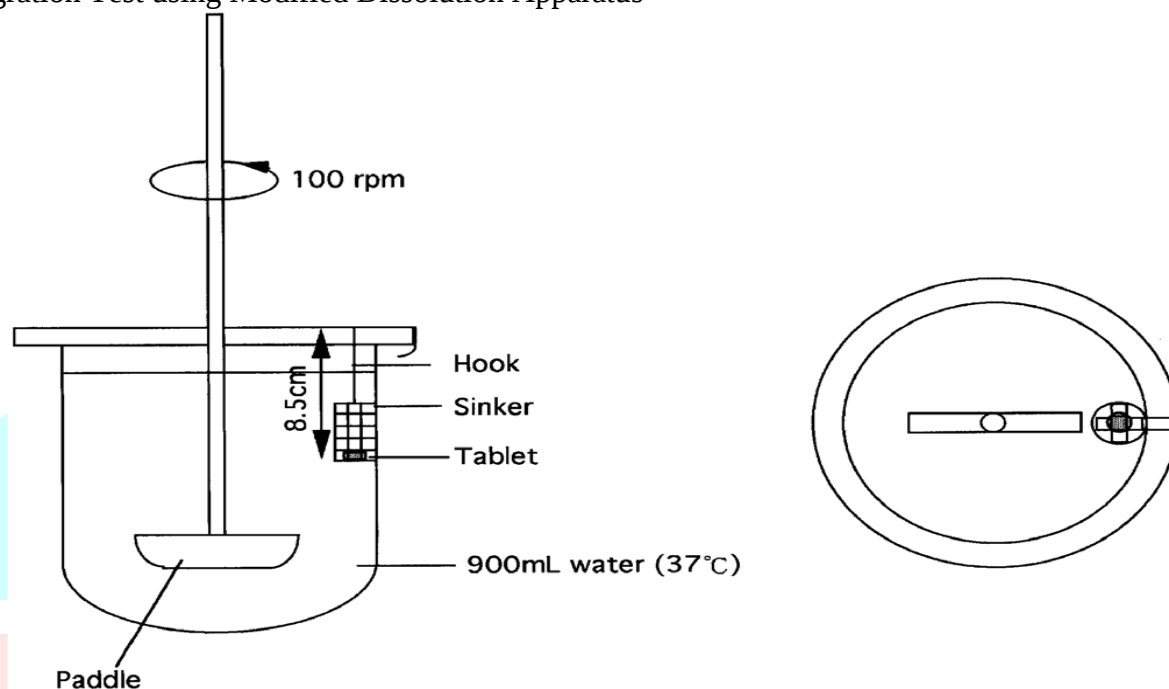


Fig.3 Schematic view of modified dissolution apparatus for disintegration test

suggested the use of a modified dissolution apparatus, instead of the disintegration apparatus as shown in Fig.3 In this experiment, 900 ml of water maintained at 37 °C as the disintegration fluid and a paddle at 100 rpm as stirring element were used. Disintegration time was noted when the tablet disintegrated and passed completely through the screen of the sinker (3–3.5 mm in height and 3.5–4 mm in wiODTh, immersed at a depth of 8.5 cm from the top with the help of a hook). This method was useful in providing discrimination among batches which was not possible with the conventional disintegration apparatus.

Disintegration Test on Wire Cloth Motohiro et al., carried out disintegration test by placing the ODT on a wire cloth No. 10 and dropped water on it at a rate of 4 ml/min. The time required by the tablet to completely pass through the wire cloth was noted as disintegration time⁵. Disintegration Test with CCD Camera Morita et al., developed a sophisticated disintegrating test apparatus equipped with a CCD camera. This apparatus is divided into two distinct sections, a disintegration component and a measurement device. The mode of measurement involves the continuous monitoring and recording of disintegration time course by obtaining pictures through the CCD camera, which are simultaneously transferred into a computer and stored. The speciality of this apparatus lies in the combination of detailed pictures obtained by the CCD camera and the calculation capabilities of the computer.

The disintegration apparatus consists of a plastic cell partitioned into two parts: one component comprises of an inner tank containing the stirring bar, the grid fabricated from stainless-steel and 200 ml of distilled water as disintegration medium maintained at 37±2 °C; the second component is an outer tank, which functions as a water bath heated at 37±1 °C (Fig.4) via circulation of thermostated water. The grid consists of three hollow areas, equidistant from the center, in which the tablets are positioned using a support to avoid their displacement during the test (Fig. 5).

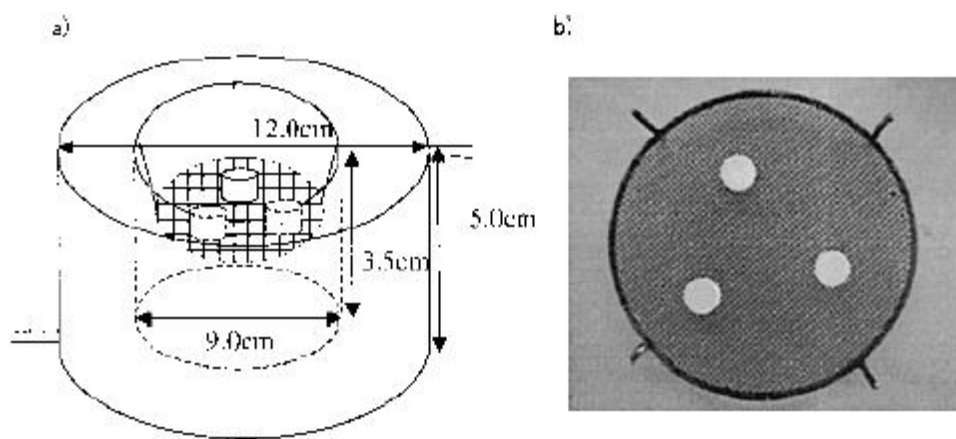


Fig. 4. Plastic Disintegration Cell (a) and Tablet Support Grid with Three RODT (b)

The measurement apparatus consists of a CCD camera and a computer. The CCD camera is positioned in such a manner that the top surface of the three tablets can be seen on the camera's screen. The disintegration time course can be analyzed graphically with the data obtained using this equipment. It is especially useful for very fast dissolving. However, this method has a limitation of absence of any mechanical stress, as the ODT placed in the oral cavity receives some mechanical stress produced by the tongue⁵.

Disintegration Test on Shaking Water Bath

Fu et al., conducted the disintegration test by placing the ODT in a glass cylinder fitted with 10 mesh at its base. This set up was further placed in a shaking water bath operated at 150 rpm. 1 ml of purified water maintained at 37 °C temperature was used as medium. The critical parameters of this method were the operational speed of shaking water bath and volume of the medium⁵.

Disintegration Test with Rotary Shaft Method In another study, Narazaki et al., proposed a better disintegration method for ODT as shown in Fig. 1.5 (a). In the experimental method, the ODT was placed on the wire gauze (D), slightly immersed in the medium, and then compressed by a rotary shaft (E) which was employed to provide mechanical stress on the tablet by means of its rotation and weight. Purified water at temperature 37 °C was used as the medium. The critical parameters of the proposed method were the rotation speed and the mechanical stress. Using this new method, it would be possible to predict a more realistic disintegration rate in human. The compression force can be easily adjusted using the weight (A). The rotary shaft crushes the ODT which disintegrates into the medium. The endpoint was measured visually using a stopwatch⁵.

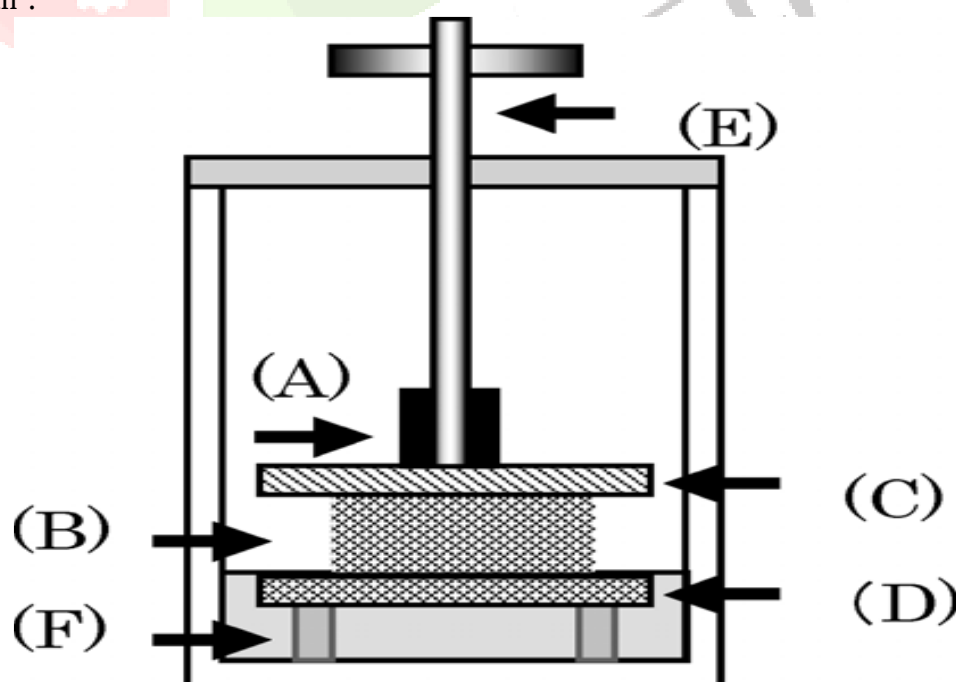


Fig. 5 Apparatus of rotary shaft method for ODT (A) weight, (B) ODT, (C) wetting sponge, (D) wire gauze, (E) rotary shaft, (F) medium.

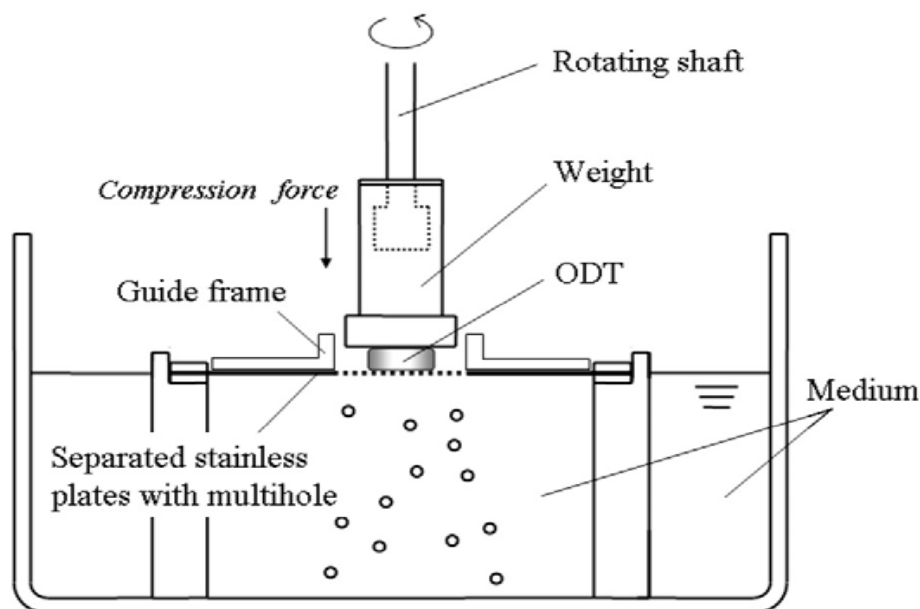


Fig. 6 improved rotary shaft apparatus

The above mentioned apparatus was modified by Harada et al., by placing a sponge at the surface of shaft weight to increase friction with the ODT (Fig. 6). Therefore, the weight transmits the torque of the rotating shaft to the ODT and grinds it on the stainless steel perforated plate which is used in place of wire gauge. The electrodes are attached on each side of the plate. The rotation speed and weight were optimized to set the mechanical pressure. When the weight makes contact with separated plates, the electric sensor conveys a signal that indicates the end point of the disintegration test of the ODT⁵.

Disintegration Test using Texture Analyzer

In another study, a texture analysis apparatus was used to measure the start and end time points of tablet disintegration. The set up is shown in Fig. 7. A constant penetration force was applied to tablets via a cylindrical flat-ended probe. The tablet, under constant force, is immersed in a defined volume of distilled water and the time is plotted against the distance, which the probe travelled into the tablet. Typical time–distance profiles, generated by the texture-analysis software, enabled the calculation of the starting and ending time of disintegration⁵.

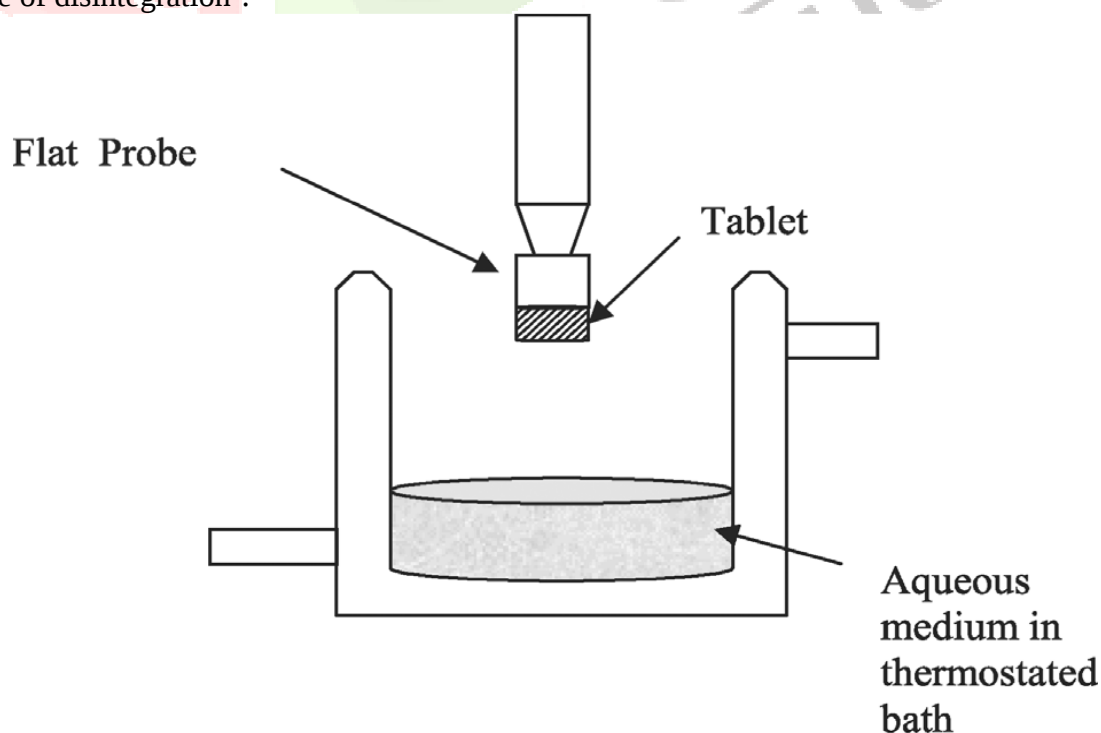


Fig 7. Texture analyzer apparatus for disintegration test

Disintegration Test using ElectroForce® 3100

An instrument “ElectroForce® 3100” has recently been designed by the Bose corporation with an objective to simulate the disintegration condition of the ODT in mouth. It is based on application of low force to measure small displacements and disintegration rate as a function of manufacturing process of a variety of ODT (Fig 8). The instrument typically consists of a lower plate to hold the tablet on which a force of about 10 mN is applied followed by addition of approximately 5 ml of water maintained at 37 °C. It has the advantage of providing better resolution than those available instruments with moderate to high force test. This is the first equipment of its type which is available in the market for evaluation of OODT. This tabletop system can be used by the manufacturers and regulatory agencies to monitor and evaluate the different fabrication technologies of ODT. Some of these new methods have been able to produce satisfactory discrimination between tablets of different types and could perhaps be taken into consideration as an effective method for evaluation of disintegration time of ODT⁵.



Fig. 8 ElectroForce® apparatus for Disintegration test A. OODT mounted on test plate before loading. B. OODT after completion of Disintegration test

g) Dissolution Testing of Dispersible Tablets

The conventional method of dissolution could be extended to in-vitro evaluation of ODT. The dissolution conditions for the reference listed drugs available in USP can be utilized for preliminary in-vitro studies to mimic better in-vivo conditions. Apart from the above, multimedia dissolution studies in various buffer solutions of different pH viz. 0.1 N HCl; pH 4.5 and 6.8 buffers should be carried out for interpretation of their in-vivo performance and pharmaceutical equivalence. USP apparatus II (paddle) with a speed of 50 rpm seems to be most suitable and common choice with appropriate dissolution media volume to maintain sink condition. Typically, the dissolution of ODT is very fast when using USP monograph conditions and therefore, under such conditions the dosage forms behave almost equally. Hence, slower paddle speeds may be employed to obtain a profile and better discrimination among various batches prepared during the developmental stage. In case of tablets approaching or exceeding one gram weight and containing relatively dense insoluble particles, there are the chances of heap formation at the bottom of the dissolution vessel. Under such a condition, although the tablet disintegrates completely, there is a significant reduction in the apparent dissolution rate. However, this issue can be resolved by using higher paddle speed of 75 rpm. The USP I (basket) apparatus may have application for certain ODT which disintegrate into particles with floating tendency. However, tablet fragments or disintegrated tablet masses may become trapped on the inner top side of the basket at the spindle where little or no effective stirring occurs, yielding irreproducible dissolution profiles. In that case, a higher basket rotation speed of 100 rpm is recommended for quality assurance purpose while the formulation should be evaluated on the basis of a separate discriminatory disintegration test as listed above⁶.

Dissolution Test for ODT with Taste-Masking Approaches

Drug substances with bitter or objectionable taste in any orally-administered dosage form, including suspensions and chewable tablets are required to be suitably taste masked. The taste masking of the dosage

form may be carried out using multiple approaches including use of taste masking flavors and sweeteners, pH dependent/independent polymer coating of drug particles or complexation using ion exchange resins or cyclodextrins. Though the use of flavors and sweeteners do not require special attention, the other taste-masking approaches greatly influence dissolution method development, specifications and testing. In such cases, the pH of the dissolution media plays a vital role in either the dissolution of the pH sensitive polymer or the release of the drug from the ionic complexes. Coated drug microparticles for controlled-release purpose, where bitter taste of drug is automatically masked, can also be incorporated in ODT. Here, the in-vitro dissolution study condition would be similar to that for a controlled release dosage form along with a discriminatory disintegration test to evaluate the disintegrating properties of the system. The disintegration time of ODT in a dissolution vessel is generally less than thirty seconds and therefore, is not an important factor in the resulting dissolution profile in terms of discrimination. Thus, the in-vitro dissolution study is carried out to assure the complete release of the drug in the media within the stipulated time period. Based on the functionality of the dosage form, single point dissolution is sufficient for an immediate release dosage form while a multi point dissolution profile is required for the evaluation of a controlled release system. However, it is important to observe the tablet's disintegration pattern and behavior of the disintegrated particles during the dissolution test for a better understanding of the role of the excipients that are used for the purpose⁷.

h) Evaluation of Effectiveness of Taste Masking

The formulation's organoleptic properties like taste, mouth-feel and appearance are of considerable importance in differentiating products in the market and can ultimately determine the success of a product. The following discussion is focused on the in-vitro and in-vivo methods for evaluation of the taste masking property⁸.

In-vivo Method

The in-vivo taste evaluation consists of a double blind crossover study, carried out on a trained taste panel of healthy volunteers with sound organoleptic senses, with their prior consent. On placing the dosage form in the oral cavity, the disintegration time is noted after which it is further held in mouth for 60 sec by each volunteer, and the bitterness level is recorded against pure drug (control) using a numerical scale. After 60 sec, the disintegrated tablet is spat out and the mouth is rinsed thoroughly with mineral water.

The numerical scale bears the following values: 0 = tasteless, 0.5 = aftertaste, 1.0 = slight, 1.5 = slight to moderate, 2.0 = moderate, 2.5 = moderate to strong, 3 = strong and 3+ = very strong. Along with the taste evaluation, a simultaneous observation of mouth feel (grittiness or smoothness) should also be noted to assess the quality of the product. This pharmaceutical taste assessment typically requires a large, trained taste panel and sophisticated interpretation. The tests may require the similar health safeguards as for a clinical trial especially for potent drugs like steroids and antipsychotics. Overall, a properly conducted taste trial adds huge investment of time and money to the product development process. Therefore, a well designed in-vitro taste masking evaluation technique would be a valuable alternative⁹.

In-vitro Method

The conventional in-vitro method of dissolution study lacks relevance to simulate the behavior of an ODT in the buccal cavity, due to excessively large dissolution media volume. Therefore, a more relevant method was developed in our laboratory wherein 5 ml of pH 6.8 phosphate buffer (to simulate salivary pH and volume) was used to study the taste masking efficiency of risperidone resinate complex. Risperidone resinate equivalent to 4mg of risperidone was placed in two 25 ml glass bottles. 5 ml of the buffer solution was then added and the bottles were allowed to stand for 60 sec and 120 sec, respectively. After the specified time, the suspensions were filtered using 0.45 μ nylon filters. The filtrates were analyzed for drug content. The test was performed in triplicate. It was found that 2.5% of drug was released in 120 secs. The bitterness threshold of risperidone is 25 μ g/ml, while the concentration of the drug released in our study was 20 μ g/ml in 120 secs which is insufficient to impart bitterness. Moreover, the disintegration time of the prepared ODT was 20 secs which would be an added advantage in further reducing the release of drug in the oral cavity. However, a very fast drug release was observed in 500 ml of 0.1N HCl using USP dissolution apparatus II at 50 rpm (about 92% of drug released in 5 mins). The pharmaceutical taste assessment usually demands large panels and elaborate analysis, raises safety and scheduling issues, and can be time consuming and expensive.

These challenges were overcome with the invention of a breakthrough electronic sensor array technology, the "E-tongue". This is a sensor device for recognition (identification, classification, and discrimination), quantitative multicomponent analysis and artificial assessment of taste and flavor. This unique device helps

to considerably reduce the developmental time and costs, subjectivity, bias and safety concerns. The E-tongue mimics the three levels of biological taste recognition: the receptor level (taste buds in humans, probe membranes in the E-tongue); the circuit level (neural transmission in humans, transducer in the E-tongue) and the perceptual level (cognition in the thalamus in humans, computer and statistical analysis in the E-tongue). At the receptor level, the E-tongue uses a seven-sensor probe assembly to detect the dissolved organic and inorganic compounds. The probes consist of a silicon transistor with proprietary organic coatings, which govern the probe's sensitivity and selectivity. Measurement is done potentiometrically. Each probe is cross-selective to allow coverage of full taste profile. At the circuit level, the system samples, quantifies and records potentiometer readings. At the perceptual level, taste cognition happens in the computer, whereas the E-tongue's statistical software interprets the sensor data into taste patterns. Depending on the study design, data analysis can produce a variety of informations. This electronic sensor was employed for taste optimization of ODT prepared by lyophilization process (Zydis technology) by Cardinal Health¹⁰.

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