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## TASTE MASKING BY INCLUSION COMPLEXATION: A REVIEW

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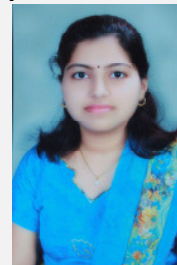
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### ABSTRACT

The role of technologies related to formulation of effective drug delivery systems which enhanced patient compliance is unique and fascinating. Over the long period of time, it has been observed that more than 50 percent of Pharmaceutical products are orally administered for several reasons. Many of these products contain drugs which have an unpleasant taste, often very bitter. The major consequence of the bitter taste is to restrict greatly the further development of oral preparations and clinical applications of these drugs. It is important to mask the unpalatable taste of a drug in order to improve the product quality. This will also increase the value of the finished product as well as patient compliance, especially where infants, children and elderly are concerned. Administration of an oral drug delivery system having bitter taste and acceptable level of palatability has always been a challenge in developing a formulation for pediatric and geriatric purpose. The bitterness of drug or drug product is minimized or eliminated by various physical, chemical and physiological means such as use of flavors, sweeteners, amino acids and by using various techniques such as lipophilic vehicles, coating, inclusion complexation, ion exchange, effervescent agents, rheological modification, solid dispersion system, group alteration and prodrug approach, freeze drying process, wet spherical agglomeration technique and continuous multipurpose melt technology.

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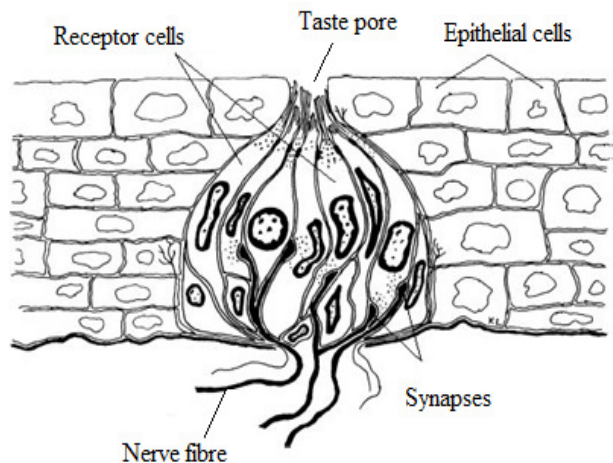
### Key Words

$\beta$ -CD, Inclusion complexation,  
Taste bud, Taste masking  
approaches

## INTRODUCTION

### The sense of taste

Taste is the ability to respond to dissolved molecules and ions “gatekeeper to the body”. Human detects taste with taste receptor cells that are clustered in to onion-shaped organs called taste buds. Each taste bud has a pore that opens out to surface of the tongue enabling molecules and ions taken into the mouth to reach the receptor cells inside.<sup>1</sup> The figure of taste bud is shown in following figure no. 1.



**Figure 1. A taste bud**

Human have around 10,000 taste buds which appear in fetus at about three months. A single taste bud contains 50-100 taste cells. Each taste cells receptors on its apical surface. These are transmembrane proteins which bind to the molecules and ions that give rise to the four primary taste sensations namely: salty, sour, sweet and bitter. Recently, a fifth basic taste umami has been discovered. The umami is the taste of certain amino acids (e.g. monosodium glutamate). There is often correlation between the chemical structure of a compound and its taste. Low molecular weight salts tend to taste salty where as high molecular weight salts tend toward bitterness. Nitrogen containing compounds, such as alkaloids, tend to be quite bitter. Organic compounds containing hydroxyl groups tend to become increasingly sweet as number of OH group increase.<sup>2</sup>

Receptor mechanism involves initial depolarization at apical receptor site, which causes local action potential in receptor cell. This in turn causes synaptic activation of the primary sensory neuron. Four

basic tastes are confirmed to specific regions of tongue (Table1). Threshold for taste is a minimum concentration of a substance that evokes perception of a taste. The following Table 1 gives the threshold concentration of four primary taste sensations. It can be observed that tongue is 10,000 times more sensitive to the bitterness of quinine than to sweetness of sugar. Saccharine, on this scale would rate about 0.001%.<sup>3</sup>

**Table 1:** Specific area of tongue and threshold concentration for primary taste sensations

Taste	Area of tongue	Threshold concentration
Sweet(sucrose)	Tip of tongue	0.5%
Salt(NaCl)	Tip and sides of tongue	0.25%
Sour(HCl)	Sides of tongue	0.007%
Bitter(Quinine)	Back of tongue	0.00005%

### Pharmaceutical approaches used to mask the taste of bitter drugs

- Addition of flavouring and sweetening agents.
- Microencapsulation
- Ion exchange.
- Inclusion complexation.
- Granulation.
- Adsorption.
- Prodrug approach.
- Bitterness inhibitor.
- Multiple emulsion technique.
- Gel formation.
- Miscellaneous.

### Addition of flavouring and sweetening agents

This technique is the foremost and the simplest approach for taste masking, especially in the case of pediatric formulations, chewable tablets, and liquid formulations. But this approach is not very successful for highly bitter and highly water-soluble drugs. Monosodium Glycyrrhizinate together with flavors has been used to mask the bitter taste of Guaifenesin.<sup>4,5</sup>

### Microencapsulation

Microencapsulation as a process has been defined by Bokan<sup>6</sup> as a means of applying relatively thin coating to small particles of solid, droplets of liquid

and dispersion. This process can be used for masking of bitter tasting drugs by Microencapsulating drug particles with various coating agents. Coating agents employed include Gelatin, Povidone, HPMC, Ethylcellulose, Bees wax, Carnauba wax, Acrylics and Shellac. Bitter-tasting drugs can be first encapsulated to produce free flowing microcapsules, which are then blended with other excipients and compressed into tablets. Microencapsulation also increases the stability of the drug. It can be accomplished by a variety of methods, including air suspension, coacervation-phase separation, spray drying and congealing, pan coating, solvent evaporation and multi-orifice centrifugation techniques. Among these, coacervation-phase separation technique appears to be more relevant and suitable for taste-masking applications.<sup>7</sup>

#### **Ion exchange**

Ion exchange resins are water insoluble, cross-linked polymers containing salt forming groups in repeating position on the polymer chain. Drug can be bound to the ion exchange resin by either repeated exposure of the resin to the drug in a chromatographic column or by prolonged contact of resin with the drug solution. The resins form insoluble adsorbates or resinsates through weak ionic bonding with oppositely charged drugs. The exchange of counter ions from resin is competitive. Most of the bitter drugs have amine as a functional group, which is the cause of their obnoxious taste. If the functional groups are blocked by complex formation the bitterness of the drug reduces drastically.<sup>8,9,10</sup>

#### **Granulation**

Granulation is a common processing step in the production of tablet dosage form. This step can be exploited as a mean for taste masking of slightly bitter tasting drug. Some saliva insoluble polymers can also act as binding agent, granules prepared from these polymers show less solubility in saliva and thus taste could be masked. Granulation lowers the effective surface area of the bitter substance that come in contact with the tongue upon oral intake. But this reduction in surface area of bitter substance may or may not be effective in masking the bad taste. Taste masked granules, prepared from saliva insoluble polymer, can be

formulated in various type of tablet dosage form, e.g., rapidly disintegrating tablet and chewable tablet. Taste masked granules of bitter tasting drug Pirenzepine and Oxybutynin have been prepared by the extrusion using Aminoalkylmethacrylate copolymer.<sup>11,12</sup>

#### **Adsorption**

Adsorbate of bitter tasting drug can be considered as the less saliva soluble versions of these drugs. Adsorption involves preparing a solution of the drug and mixing it with an insoluble powder that will absorb the drug, removing the solvent, drying the resultant powder, and then using these dried adsorbates in the preparation of the final dosage form. Many substrates like Veegum, Bentonite, Silica gel and silicates can be used for the preparation of adsorbate of bitter drugs. Loperamide and Phenyl propanolamine have been adsorbed on Magnesium aluminium silicates also known as Veegum F to prepare bitter taste masked suspension of these drugs.<sup>13</sup>

#### **Prodrug approach**

A prodrug is chemically modified inert drug precursor which upon biotransformation liberates the pharmaceutically active parent compound. A combination of factors is perhaps operative in the demonstration of a taste response molecular geometry is one of them, for e.g. bitterness of a molecule, may be due to the efficiency of the taste receptor substrate adsorption reaction, which is related to the molecular geometry of the substrate.<sup>14,15</sup>

#### **Bitterness inhibitor**

The development of a specific universal inhibitor for bitter taste has been widely required in the fields of taste physiology and Pharmaceutical sciences, but no such inhibitors has been available. One difficulty in discovering of universal inhibitor for bitter taste is that substances that inhibit bitterness of one compound will not influence the bitterness of a second because many different classes of compound impart bitterness. Sodium salts such as Sodium chloride, Sodium acetate and Sodium gluconate have been shown to be potent inhibitors of some bitter compounds. The mechanism is not known, however, research shows that sodium act at peripheral taste level rather than a cognitive effect.<sup>16,17</sup>

#### **Multiple emulsion technique**

A novel technique for taste masking of drugs employing multiple emulsions has been prepared by dissolving drug in the inner aqueous phase of w/o/w emulsion under conditions of good shelf stability. The formulation is designed to release the drug through the oil phase in the presence of gastrointestinal fluid.<sup>18</sup>

### Gel formation

Water insoluble gelation on the surface of tablet containing bitter drug can be used for taste masking. Sodium alginate has the ability to cause water insoluble gelation in presence of bivalent metal ions. Tablet of Amiprolsehydrochloride have been taste masked by applying an undercoat of Sodium alginate and overcoat of Calcium gluconate. In presence of saliva, Sodium alginate reacts with bivalent calcium and form water insoluble gel and thus taste masking achieved.<sup>19</sup>

### Miscellaneous

#### By effervescent agents

Effervescent agents have been shown to be useful and advantageous for oral administration of drugs and have been employed for use as taste masking agents for dosage forms that are not dissolved in water prior to administration. A chewing gum composition of bitter medicament was formulated to supply the medicament to oral cavity for local application or for buccal absorption.<sup>20,21</sup>

#### Rheological modification

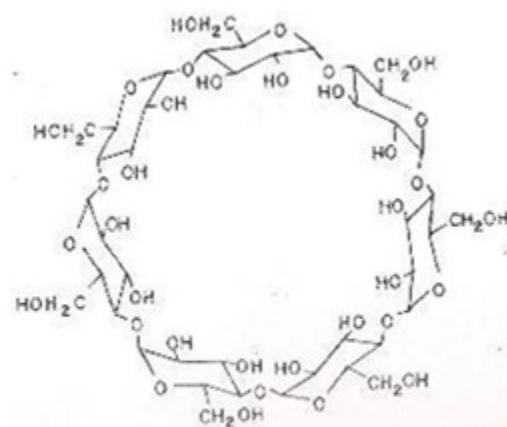
Increasing the viscosity with rheological modifier such as gums or carbohydrates can lower the diffusion of bitter substances from the saliva to the taste buds. Acetaminophen suspension can be formulated with Xanthan gum (0.1-0.2%) and Microcrystalline cellulose (0.6-1%) to reduce bitter taste. The antidepressant drug Mirtazapine is formulated as an aqueous suspension using Methonine (stabilizer) and Maltitol (thickening agent). Maltitol is stable in the acidic pH range of 2 to 3 and besides masking the unpleasant taste of the drug, it also inhibits its undesirable local anaesthetic effect.<sup>22,23</sup>

#### Taste masking by inclusion complexation

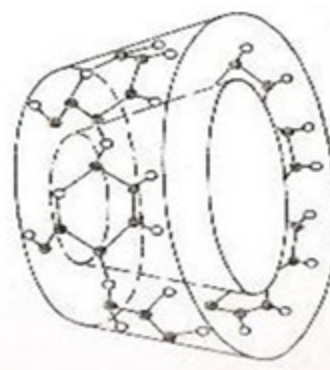
A complex in which one component (the host) forms a cavity or in the case of a crystal, a crystal lattice containing spaces in the shape of long tunnels or

channels in which molecular entities of a second chemical species (the guest) are located.

Cyclodextrins (CDs) are cyclic oligosaccharides containing six ( $\alpha$ -CD), seven ( $\beta$ -CD) or eight ( $\gamma$ -CD)  $\alpha$ -1,4-linked glycopyranose units, with a hydrophilic hydroxyl group on their outer surface and a hydrophobic cavity in the center. Owing to lack of free rotation about the bonds connecting the glucopyranose units, the cyclodextrins are not perfectly cylindrical molecules but are toroidal or cone shaped. Based on the architecture, the *primary* hydroxyl groups are located on the narrow side of the torus while the secondary hydroxyl groups are located on the wider edge (Figure 1).<sup>24</sup> The chemical structure and toroidal shape of  $\beta$ -cyclodextrin molecule is shown below in Figure no. 2.



(a)



(b)

**Figure 2(a):** The chemical structure and (b) the toroidal shape of the  $\beta$ -cyclodextrin molecule.

The most common cyclodextrins are  $\alpha$ -cyclodextrin ( $\alpha$ -CD),  $\beta$ -cyclodextrin ( $\beta$ -CD) and  $\gamma$ -

cyclodextrin( $\gamma$ -CD) which consist of six, seven and eight glucopyranose units respectively. But due to steric factors, cyclodextrins having fewer than six glucopyranose units cannot exist, cyclodextrins containing nine, ten, eleven, twelve and thirteen glucopyranose units, which are designated  $\delta$ -,  $\epsilon$ -,  $\zeta$ -,  $\eta$ - and  $\theta$ -cyclodextrin, respectively have been reported. The chemical and physical properties of the four most common cyclodextrins are given in Table 1.<sup>25</sup>

**Table 1:** Chemical and physical properties of  $\alpha$ ,  $\beta$ ,  $\gamma$  and  $\delta$ -cyclodextrin

Physicochemical properties	$\alpha$	$\beta$	$\gamma$	$\delta$
No of glucopyranose units	6	7	8	9
Molecular Weight	972	1135	1297	1459
Central cavity diameter (Å)	4.7-5.3	6.0-6.5	7.5-8.3	10.3-11.2
Water solubility at 25°C (g/100 ml)	14.5	1.85	23.2	8.19

CDs are capable of forming inclusion complexes with many drugs by taking up a whole drug molecule, or some part of it, into the cavity. Such molecular encapsulation will affect many of the physicochemical properties of drugs, such as their aqueous solubility and rate of dissolution. Among the various approaches, preparation of inclusion complexes with cyclodextrin has proven to be successful in enhancing the solubility of poorly water soluble drugs. The formation of inclusion complexes, the wide variety of guest molecules is one of the most interesting properties of cyclodextrins. Molecular encapsulation may occur both in solid and in solution state. In solid state, guest molecules can be enclosed within the cavity or may be aggregated to the outside of the cyclodextrin molecule and in solution state; there is equilibrium between complexed and non-complexed guest molecules. A guest molecule experiences changes in the physicochemical properties when it gets incorporated within the cyclodextrin cavity. Changes in

the physicochemical properties provide methods to characterize whether guest molecules are really included in the cyclodextrin cavity.

The various technologies adopted to prepare the inclusion complexes of poorly water soluble drugs with CDs and an attempt was also made to highlight the potential applications, technical and economical limitations associated with this approach.<sup>26</sup>

## Approaches for making of inclusion complexes

### 1. Physical blending method

A solid physical mixture of drug and CDs are prepared simply by mechanical trituration. In laboratory scale CDs and drug are mixed together thoroughly by trituration in a mortar and passes through appropriate sieve to obtain the desired particle size in the final product. In industry scale, the preparation of physical mixtures is based on extensive blending of the drug with CDs in a rapid mass granulator usually for 30 minutes. These powdered physical mixtures are then stored in the room at controlled temperatures and humidity conditions.<sup>27</sup>

### 2. Kneading method

This method is based on impregnating the CDs with little amount of water or hydroalcoholic solutions to convert into a paste. The drug is then added to the above paste and kneaded for a specified time. The kneaded mixture is then dried and passed through sieve, if required. In large scale, the kneading can be done by utilizing the extruders and other machines. This is the most common and simple method used to prepare the inclusion complexes and it presents very low cost of production.<sup>28</sup>

### 3. Co-precipitation technique

This method involves the co-precipitation of drug and CDs in a complex. In this method, required amount of drug is added to the solution of CDs. The system is kept under magnetic agitation with controlled process parameters and the content is protected from the light. The formed precipitate is separated by vacuum filtration and dried at room temperature in order to avoid the loss of the structure water from the inclusion complex. This technique leaves drug-CD solution in very close conditions to the saturation and through abrupt changes of temperature with addition of organic solvents. It is

obtained to the precipitation of the material forming inclusion complex. The powders are obtained by rotation or filtration with heat while stirring the solution. However, due to low yield, risk of using organic solvents and longer time required for the preparation in large scale, this method is attaining little attraction in the industrial scale.<sup>29</sup>

#### **4. Solution/solvent evaporation method**

This method involves dissolving of the drug and CDs separately in two mutually miscible solvents, mixing of both solutions to get molecular dispersion of drug and complexing agents and finally evaporating the solvent under vacuum to obtain solid powdered inclusion compound. Generally, the aqueous solution of CDs is simply added to the alcoholic solution of drugs. The resulting mixture is stirred for 24 hours and evaporated under vacuum at 45°C. The dried mass was pulverized and passed through a 60-mesh sieve. This method is quite simple and economic both on laboratory and large scale production and is considered alternative to the spray drying technique.

#### **5. Neutralization precipitation method**

This method is based on the precipitation of inclusion compounds by neutralization technique and consists of dissolving the drug in alkaline solutions like sodium/ammonium hydroxide and mixing with an aqueous solution of CDs. The resultant clear solution is then neutralized under agitation using hydrochloric acid solution till reaching the equivalence point. A white precipitate is being formed at this moment, corresponding to the formation of the inclusion compound. This precipitate is filtered and dried. Acid and alkaline susceptible drugs can undergo degradation during this process is the limitation associated with this method.<sup>30</sup>

#### **6. Milling/co-grinding technique**

A solid binary inclusion compounds can be prepared by grinding and milling of the drug and CDs with the help of mechanical devices. Drug and CDs are mixed intimately and the physical mixture is introduced in an oscillatory mill and grinded for suitable time. Alternatively, the ball milling process can also be utilized for preparation of the drug-CD binary system. The ball mill containing balls of varied size is operated at a

specified speed for a predetermined time and then it is unloaded, sieved through a 60-mesh sieve. This technique is superior to other approaches from economic as well as environmental stand point in that unlike similar methods it does not require any toxic organic solvents. This method differs from the physical mixture method where simple blending is sufficient and in co-grinding it requires to achieve extensive combined attrition and impact effect on powder blend.<sup>31</sup>

#### **7. Atomization/spray drying method**

Spray-drying is a common technique used in Pharmaceuticals to produce a dry powder from a liquid phase. Another application is its use as a preservation method, increasing the storage stability due to the water elimination. This method represents one of the most employed methods to produce the inclusion complex starting from a solution. The mixture pass to a fast elimination system propitiate solvent and shows a high efficiency in forming complex. Besides, the product obtained by this method yield the particles in the controlled manner which in turn improves the dissolution rate of drug in complex form. The sufficient and efficient interaction between drug and CDs to form a perfect complex is the added advantage of atomization/spray drying method where as thermal stress and low yield of the final product are the limitations associated with this technique.<sup>32</sup>

#### **8. Lyophilization/ freeze drying technique**

In order to obtain a porous, amorphous powder with high degree of interaction between drug and CD, lyophilization/freeze drying technique is considered as a suitable. In this technique, the solvent system from the solution is eliminated through a primary freezing and subsequent drying of the solution containing both drug and CD at reduced pressure. Thermolabile substances can be successfully made into complex form by this method. The limitations of this technique are long time process and yield poor flowing powdered product. Lyophilization/freeze drying technique is considered as alternative to solvent evaporation and involves molecular mixing of drug and carrier in a common solvent.<sup>33</sup>

### 9. Microwave irradiation method

This technique involves the microwave irradiation reaction between drug and complexing agent using a microwave oven. The drug and CD in definite molar ratio are dissolved in a mixture of water and organic solvent in a specified proportion into a round bottom flask. The mixture is reacted for short time of about one to two minutes at 60°C in the microwave oven. After the reaction completes, adequate amount of solvent mixture is added to the above reaction mixture to remove the residual, uncomplexed free drug and CD. The precipitate so obtained is separated using Whatman filter paper and dried in vacuum oven at 40°C for 48 hrs. Microwave irradiation method is a novel method for industrial scale preparation due to its major advantage of shorter reaction time and higher yield of the product.<sup>34</sup>

### 10. Supercritical antisolvent technique

This method has been introduced in the late 1980s. In the supercritical fluid antisolvent technique, Carbon dioxide is used as anti-solvent for the solute but as a solvent with respect to the organic solvent. The use of supercritical Carbon dioxide is advantageous as its low critical temperature and pressure makes it attractive for processing heat-labile Pharmaceuticals. It is also non-toxic, non flammable and inexpensive and is much easier to remove from the polymeric materials when the process is complete, even through small amount of carbon dioxide remains trapped inside the polymer, it poses no danger to the consumer. Supercritical particle generation processes are new and efficient route for improving bioavailability of pharmaceutically active compounds. In addition, supercritical fluid processes were recently proposed as a new alternative method for the preparation of drug Cyclodextrin complexes. Supercritical Carbon dioxide is suggested as a new complexation medium due to its properties of improved mass transfer and increased solvating power. This method constitutes one of the most innovative methods to prepare the inclusion complex of drug with CD in solid state. This is a non-toxic method as it is not utilizing any organic solvent, fast process, maintenance cost is low with promising results, but it requires a quite high initial cost. In this technique, first the drug and CD are

dissolved in a good solvent then the solution is fed into a pressure vessel under supercritical conditions, through a nozzle. When the solution is sprayed into supercritical fluid anti-solvent, the anti-solvent rapidly diffuses into that liquid solvent as the carrier liquid solvent counter diffuses into the anti-solvent.<sup>35</sup>

**Table 2:** Taste masking of bitter drug by complexation

Drug	Complexing Agent	Dosage form
Benexate hydrochloride	Cyclodextrin	Granules
Carbopentane citrate	Cyclodextrin	Oral liquid
Chloroquine phosphate	Tannic acid	Syrup
Dimenhdrinate	Eudragit S-100	Chewable Tablet
Gymnemasylves tra	Chitosan	Oral liquid
Ibuprofen	Hydroxypropyl $\beta$ -CD	Solution

### Cyclodextrins as permeation enhancers

In spite, the solubility enhancement application, CDs can also be used as membrane permeability enhancer and stabilizing agents.<sup>36</sup> The permeability through biological membrane is enhanced by the presence of cyclodextrins. These act as permeation enhancers by carrying the drug through the aqueous barrier which exists before the lipophilic surface of biological membranes.<sup>37</sup> This can also be achieved through the double characteristics of the CDs, thus present character much lipophilic as hydrophilic.<sup>38</sup>

### Characterization of inclusion complexation in solid states

1. Thermo-analytical methods.
2. Scanning electron microscopy (SEM).
3. X-ray diffractometry and single crystal X-ray structure analysis.
4. Wettability and dissolution tests.
5. Infra-Red (I R) spectroscopy.
6. Thin layer chromatography (T L C).

#### 1. Thermo-analytical methods

Thermo-analytical methods determinewhetherthe guest substance undergoes somechange before the thermic degradation of cyclodextrin. The change of the guest substance may be melting, evaporation, decomposition, oxidation or polymorphic transition. The change of the guest substance indicates the complex formation. The effect of cyclodextrins on the thermogram obtained by DTA and DSC were observed for broadening, shifting and appearance of new peaks or disappearance of certain peaks. Changes in the weight loss wereevaluated to provide supporting evidence for the formation of inclusion complexes.

The nature of the drug and cyclodextrinsusedand method of preparation of complex havebeen found to influence the above findingconsiderably. If the interaction between thedrug and the excipient is weak, the shift inthe endothermic peak is very small.The formation of inclusion complex ofSalbutamol with cyclodextrinsby variousmethods was evaluated using DSC. TheDSC endotherm of Salbutamol at 158°C wasshifted to 150°C in the physical mixtureshowing a weak interaction. But the freeze-dried complex showed no peak around157°C indicating the formation of a trueinclusion complex.<sup>39</sup>

The thermogram of Azelaic acid revealed an endothermic peak at around 105°C,corresponding to its melting point. The thermogram of physical mixture demonstrated the melting point of Azelaic acid, indicating that an inclusion complex could not be obtained by simple blending the drug and HP- $\beta$ -CD. The inclusion complex formed by co-evaporation method did not exhibit the melting endothermic peak of Azelaic acid, indicating that Azelaic was incorporated in the HP- $\beta$ -CD cavity.

## 2. Scanning electron microscopy (SEM)

Scanning Electron Microscopy is used to study the microscopic aspects of the raw material (cyclodextrin and the guest substances, respectively) and the product obtained by co-precipitation /evaporation.<sup>40</sup> The difference in crystallization state of the raw material and the product observed under electron microscope indicates the formation of the inclusion complexes, even if there is a clear difference in

crystallization state of the raw material and the product obtained by co-precipitation. This method is inadequate to affirm inclusion complex formation.<sup>41</sup> The particle morphology of Ketoprofen, $\beta$ -cyclodextrin ( $\beta$ -CD), its physical mixtures and solid complexes were evaluated by SEM photographs.

## 3. X-Ray diffractometry and single crystal X-Ray structure analysis

Powder X-ray diffractometry may be used to detect inclusion complexation in the solid state. When the guest molecules are liquid since liquid have no diffraction pattern of their own, then the diffraction pattern of a newly formed substance clearly differs from that of uncomplexed cyclodextrin. This difference of diffraction pattern indicates the complex formation.<sup>42</sup> When the guest compound is a solid substance, a comparison has to be made between the diffractogram of the assumed complex and that of the mechanical mixture of the guest and cyclodextrin molecules.

Single crystal X-ray structure analysis may be used to determine the detailed inclusion structure and mode of interaction. The interaction between the host and guest molecules can be identified and the precise geometrical relationship can be established. This information obtained during the analysis lead to know about the formation of inclusion complexes.

## 4. Wettability and dissolution tests

The wetting of the solid phase by a solvent is always the first step of any dissolution process. Cyclodextrin complexations of the lipophilic drug often improve the wettability in water considerably, but also simple addition of  $\beta$ -cyclodextrin to non-wettable solid enhances their wettability. Three methods to characterize the wettability of solid cyclodextrin formulations include the measurement of the contact angles, powder sedimentation studies which may be carried out by layering equal amounts of the samples onto the surface of water, following their sedimentation photographically and the last method demonstrates the upward migration of a coloured front of three open tubes containing the guest compound, a mixture of the guest compound with cyclodextrin and the inclusion complex, respectively, as function of the time. When an

assumed complex is dispersed in water, very rapid dissolution rate tests are based on this observation.<sup>43</sup>

### 5. Infra-red (IR) spectroscopy

Infra-Red spectroscopy is used to estimate the interaction between cyclodextrin and the guest molecules in the solid state. Cyclodextrin bands often change only slightly upon complex formation and if the fraction of the guest molecules encapsulated in the complex is less than 25%, bands which could be assigned to the included part of the guest molecules are easily masked by the bands of the spectrum of cyclodextrin.<sup>44</sup>

### 6. Thin layer chromatography (TLC)

In Thin Layer Chromatography, the Rf values of a guest molecule diminishes to considerable extent and this helps in identifying the complex formation between guest and host molecule. Inclusion complexation between guest and host molecules is a reversible process.<sup>45,46</sup>

### Evaluation techniques

#### Sensory evaluation

Taste, to think of, is a very subjective perception. Depending on individuals, the perceived taste may vary to different degrees. If well controlled experimental set up, it is possible to accurately and reproducibly measure taste thresholds. To quantitatively evaluate taste sensation, following methods have been reported in literature.

- Panel testing (human subjects)
- Measurement of frog taste nerve responses.
- Multichannel taste sensor/ magic tongue

#### Panel testing

The panel testing is a psychophysical rating of the gustatory stimuli. In this method, a group of about 5-10 human volunteers is trained for taste evaluation by using reference solutions ranging in taste from tasteless to very bitter. Numerical values are then assigned to these levels of bitterness (e.g. 0-5). Subsequently, test solution is tasted and rated on the same scale to assess its bitterness. Literature reports panel testing in invariably all the taste-masked drugs being evaluated. The ease of the method combined with the accuracy of human perception of taste against any other gustatory

evaluation technique makes panel testing the most commonly used technique.<sup>47</sup>

#### Measurement of frog taste nerve responses

In this method, adult bull frogs are anaesthetized intraperitoneally and the glossopharyngeal nerve is then located and dissected from the surrounding tissue and cut proximally. An amplifier and an electronic integrator are used to respectively, amplify and integrate the nerve impulses. The peak height of the integrated response is then taken as the magnitude of response.<sup>48</sup>

#### Multichannel taste sensor / magic tongue

This is an automated taste sensing device to detect the magnitude of bitterness of a drug substance. The device has a transducer which is composed of several kinds of lipid/polymer membranes with different characteristics that can detect taste in a manner similar to human gustatory sensation. Taste response is transferred into a pattern composed of electric signals of membrane potentials of the receptor part. Different response electric potential pattern are obtained for substance producing different taste qualities. Recently, the technique has been applied, for the quantitative evaluation of the bitterness of some commercially available medicines. Quinine hydrochloride was taken as the standard for bitterness. Basic drug with Amino groups in the molecule such as Quinine, show a comparatively good correlation between the relative response electric potential (mV) of channels 1 or 2 of the taste sensor, which contain negatively charged membranes and the bitterness as determined by human gustatory sensations tests. Secondly, for anionic drugs, such as Diclofenac sodium or Salicylic acid, the positively charged membrane in channel 5 or 6 seemed to be useful even though they are being sour rather than bitter. For drugs with both an Amino (cationic) groups and a Carboxylic acid (anionic) group in the molecule, such as Theophylline, Caffeine and Metronidazole, the electric potential (mV) of channel 1 or 2 did not increase, even though bitterness was observed in human gustatory sensation test. Therefore, different types of membrane component will be needed for a complete evaluation of the bitterness of medicines.<sup>49,50</sup>

## Patented technologies

### 1. Zydis Technology

Zydis is a unique freeze-dried oral solid dosage form that can be swallowed without water as it dissolves instantly on tongue in less than 5 seconds. The drug is physically trapped in a water-soluble matrix, and then freeze-dried to produce a product that rapidly dissolves. As the zydis dosage form is weak in physical strength, unit is contained in peelable blister pack, which allows removal of product without damaging it.

### 2. Orasolv Technology

CIMA labs have developed Orasolv technology. The system essentially makes tablets that contain taste masked active ingredients and effervescent disintegrating agent which on contact with saliva, rapidly disintegrates and releases the taste mask active ingredient. The tablets made by direct compression at very low compression force in order to minimize oral dissolution time. The taste masking associated with Orasolv formulation is two folds. The unpleasant flavour of a drug is not merely counteracted by sweeteners or flavours; coating the drug powder and effervescence are means of taste masking in Orasolv.<sup>51</sup>

### 3. Durasolv Technology

Durasolv is CIMA's second generation fast dissolving tablet formulation. Produced in a similar fashion to that of orasolv, durasolv has much higher mechanical strength than its predecessor due to the use of higher compaction produced during tableting. The durasolv product is thus produced in a faster and more cost effective manner. One disadvantage of durasolv is that the technology is not compatible with larger doses of active ingredients, because formulation is subjected to high pressures on compaction.

### 4. WOWTAB Technology

WOWTAB technology is patented by Yamanouchi. Wow means "without water". WOWTAB is an intrabuccally soluble, compressed tablet consisting of granules made with saccharides of low and high mouldability. The combination of high and low mouldability is used to obtain a tablet of adequate hardness and fast dissolution rate. Mouldability is the capacity of the compound to be compressed.<sup>52</sup>

### 5. FlashDose Technology (Fuisz Technologies, Ltd.)

Fuisz has patented the FlashDose technology. The FlashDose technology utilizes a unique spinning mechanism to produce a floss-like crystalline structure, much like cotton candy. This crystalline sugar can then incorporate the active drug and be compressed into a tablet. FlashDose tablet consists of self-binding sheaf matrix termed "floss". The procedure has been patented by Fuisz and known as "Shearform". Interestingly, by changing the temperature and other conditions during production, the characteristics of the product can be altered greatly.

#### A. Shearform Technology™

The technology is based on the preparation of floss that is also known as 'Shearform Matrix', which is produced by subjecting a feed stock containing a sugar carrier by flash heat processing. In this process, the sugar is simultaneously subjected to centrifugal force and to a temperature gradient, which raises the temperature of the mass to create an internal flow condition, which permits part of it to move with respect to the mass.

#### B. Ceform technology™

In ceform technology microspheres containing active ingredient are prepared. The essence of ceform microsphere manufacturing process involves placing a dry powder, containing substantially pure drug material or a special blend of drug materials plus other pharmaceutical compounds, and excipients into a precision engineered and rapidly spinning machine.<sup>53</sup>

### 6. Flashtab Technology

This technology involves the preparation of a rapidly disintegrating tablet which consists of an active ingredient in the form of microcrystals. Drug microgranules may be prepared by using the conventional techniques like microencapsulation, coacervation and extrusion-spheronization. The microcrystals or microgranules of the active ingredient are added to the granulated mixture of excipients prepared by wet or dry granulation and compressed into tablets.

### 7. Oraquick Technology

The oraquick fast dissolving tablet formulation utilizes a patented taste masking technology

by K. V. Pharmaceutical Company, who claim that its taste masking technology i.e. microspheretechnology (micromask) has superior mouthfeel over taste masking alternatives. The tastemasking process does not utilize solvents of any kind and therefore leads to faster and more efficient production. Tablet with significant mechanical strength without disrupting taste masking are obtained after compression.<sup>54</sup>

#### 8. FastWrap system

BioProgress had developed novel tablet cores with a high disintegration profile that were easily coated using the TabWrap finishing process. The FastWrap system combines the TabWrap process with the company's patented novel tablet core technology to create coated tablets that can rapidly disintegrate and dissolve, allowing for a faster onset of action. The FastWrap technology can also be used to manufacture film-flavoured orally disintegrating tablets.

#### 9. NanoCrystal Technology

RDT, Elan's proprietary NanoCrystal technology can enable formulation and improve compound activity and final product characteristics. Decreasing particle size increases the surface area, which leads to an increase in dissolution rate. This can be accomplished predictably and efficiently using NanoCrystal technology.<sup>55</sup>

#### CONCLUSION

Inclusion complex with cyclodextrins is the most attractive technique to mask the bitter taste of drug and to enhance aqueous solubility of poorly soluble drugs. CDs, act as the useful solubilizer enabling both solid/liquid oral and parenteral dosage forms. Solid binary system of drug and CDs are capable to modify the physicochemical properties of drugs such as solubility, particle size, crystal habit, thermal behavior, taste and there by forming a highly water soluble amorphous forms.

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