2.1. REVIEW OF PAST WORK ON TASTE MASKING

Szejtli et al (2005) determine the extent of complexation of the guest molecule (percentage of complexation) at the equilibrium. The $K_{ass}$ for most drug/CD complexes at 36°C buccal cavity temperature is between $10^2$ and $10^4$ mol$^{-1}$. If the unit dose (of a sublingual or chewing tablet, chewing gum) with a bitter drug (molecular weight of about 150, forming a 1:1 complex with βCD) is approximately 10 mg then the βCD can be taken in a 5- or even 10-fold molar excess. Therefore, the complexation of the bitter drug is completed very rapidly. Only dissolved substances have taste and only CD complexable drug molecules can become debittered by CDs. Bitter, astringent components of foods (e.g. soya), beverages (e.g. naringin in citrus fruit juice, or chlorogenic acid and polyphenols in coffee) cigarette smoke (nicotine) also can be complexed and their taste reduced or fully eliminated.

Serfert et al (2010) describe study was to evaluate the suitability of defined odour attributes for the sensory evaluation of bulk fish oil and reconstituted microencapsulated fish oil as well as the active modification of the sensory profile during storage. Reconstituted sodium caseinate-based microcapsules exhibited a lower fishy odour during storage than did n-octenylsuccinate-derivatised starch-based microcapsules, probably due to the oxidative status. Flavour binding of caseinate may be of minor importance in reconstituted microencapsulated fish oil. Improvement of the sensory profile was achieved by the addition of an odour-masking compound (β-cyclodextrin) or flavouring (vanillin and apple flavour).

Folch et al (2010) describes the stoichiometry of TC complexes was determined and in all cases was 1:1. Stability constants were determined and their antioxidant capacity against reactive oxygen species (ROS) studied by means of the ORAC-fluorescein (ORAC-FL) and the ORAC-pyrogallol red (ORAC-PGR) assay. The antioxidant capacity of these TC in aqueous solution in the absence and presence of βCDs was studied using Multi-Detection Microplate Reader. The antioxidant reactivity mainly depends of the inclusion modes of the TC in the βCDs cavity. The difference between ORAC-PGR values for the same TC show that the inclusion structures should be different, maybe leading the same number of hydrogen atoms exposed (ORAC-FL values) outside or in the borders of βCDs cavity.
Katsuragi et al (2010) describes the effects of various lipoproteins on the taste sensation to various stimuli in humans by a psychophysical method. Using PA-LG, the effects on taste sensation to various stimuli were examined. The inhibition of bitter taste was completely reversible. Among various drugs, basic and hydrophobic substances such as quinine, denatortium and propranolol have low taste thresholds and are said to be the most bitter. PA-LG most effectively suppressed the bitter taste of such substances. PA originates from soybeans and the proteins used except for bovine serum albumin originate from milk or eggs, and hence the lipoproteins can be safely used to mask the bitter taste of drugs.

Ammanag et al (2010) purpose of this research was to develop a bitterless oral disintegrating tablet of Dicyclomine hydrochloride. Taste masking was done by complexing Dicyclomine hydrochloride with Eudragit =E-100. Drug polymer complexes were prepared in the ratio 1:1, 1:2 and 1:3 by solvent evaporation method and 1:3 ratio was selected which shows least drug release in SSF (4.9 ± 0.31%). Three superdisintegrants were used while preparing the tablets e.g. crosscarmellose sodium, sodium starch glycolate and crospovidone. Tablets that were formulated by direct compression method using Crospovidone (6%) i.e. optimized formulation F9 exhibited quicker disintegration of tablets than compared to those of Crosscarmellose sodium and Sodium starch glycolate. The stability studies were carried out according to ICH guideline which indicates that the selected formulation was stable.

Khattab et al (2007) prepared hyoscine butylbromide (a drug with bitter taste) tablets that can rapidly disintegrate in saliva. The granules were prepared by the extrusion method using aminoalkyl methacrylate copolymers (Eudragit E-100). The drugs dissolved rapidly in medium at pH 1.2 in a dissolution test while none of the drugs dissolved from the granules (% of dissolved < 5%) even after 8h at pH 6.8. The prepared tablets (compressed at 500 kgf) containing the taste-masked granules have significant strength (crushing strength was 3.5 kg), and a rapid disintegration time (within 30 sec) was observed in the saliva of healthy volunteers. None of the volunteers sensed any bitter taste after the disintegration of the tablet that contained the taste-masked granules.
2. Literature Survey

2.2. REVIEW OF PAST WORK ON SOLUBILITY AND BIOAVAILABILITY

Aithal et al (2005) have prepared inclusion complexes of norfloxacin with β-cyclodextrin in different ratio of norfloxacin: β cyclodextrin (1:5, 1:1, 1:2 w/w and 1:1M) by different methods (Kneading, physical mixture and neutralization). The 1:1M neutralization complex gives maximum value of both UV-absorption (a= 3 times) and fluorescence emission (K= 4-times) as compared to physical mixture and kneading complexes.

Belgamwar et al (2001) have prepared occlusion complexes of Furazolidone with various cyclodextrins such as α, β, γ-cyclodextrins and their hydroxypropyl derivatives to enhance solubility and dissolution rate of drug. Complexes were prepared by kneading method. The complexes with cyclodextrins and their derivatives enhances the solubility and dissolution rate of Furazolidone.

Belgumwar et al (2002) have prepared inclusion complexes of griseofulvin with various cyclodextrins and their hydroxypropyl derivatives have attempted to enhance solubility and dissolution rate of drug inclusion complexes prepared by kneading method. It has been observed that formation of inclusion complexes with cyclodextrins and their derivatives enhances the solubility and dissolution rate of griseofulvin.

Francois et al (2003) prepared a mucoadhesive, cyclodextrin-based vaginal cream formulation of itraconazole with hydroxypropyl β-cyclodextrin. An aqueous phase was prepared by solubilizing itraconazole with HCl in the presence of propylene glycol and then adding an aqueous solution of hydroxypropyl β-cyclodextrin. After pH adjustment, the itraconazole/ hydroxypropyl β-cyclodextrin solution was added to the oil phase and the desired cream containing 1%, 2% and 2.5% drug obtained by homogenization. Primary irritation and sub-chronic toxicity studies using a rabbit vaginal model indicated formulation was safe, well tolerated and retained in vaginal space. Studies suggested that an hydroxypropyl β-cyclodextrin based, emulsified wax cream formulations was a useful and effective dosage form for treating vaginal candidiasis.

Gupta et al (2004) have prepared methotrexate prodrugs of α and β-cyclodextrin. The primary hydroxy group of α and β-cyclodextrin block the acidic group and the hydrolysis of
cyclo-dextrin conjugates in colon is confirmed by hydrolysis kinetic studies in rat fecal material and the conjugate showed good masking ulcerogenic potential of free drug.

**Indop et al (2002)** have prepared inclusion complexes of quercetin with hydroxypropyl β-cyclodextrin in 1:5 molar ratio. The maximum tolerated dose corresponding to the Ld10 was >400 mg/Kg of hydroxypropyl β-cyclodextrin complex of quercetin obtained after single intraperitoneal application which proved to be less toxic than quercetin. There was no apparent toxicity to bone marrow of irradiated Swiss mice. Previously administered HPBC complex of quercetrin. The ability to selectively target quercetin via its cyclodextrin inclusion complex against cancer growth could improve the therapeutic effectiveness of cyclodextrin preparation as well as reduce adverse effect associated with quercetin.

**Loganathan et al (2000)** studied the effect of solid dispersion on solubility and dissolution rate of Ibuprofen. Water soluble carriers like urea, mannitol, PEG 4000 and PEG 6000 were used for preparation of solid dispersion. The solid dispersions when analysed for *in-vitro* release showed an enhanced release of Ibuprofen in phosphate buffer (PH 7.2). 90% of the drug was reported to be released from urea and mannitol solid dispersions in 90 minutes and a release of 90% was reported in 45 minutes form urea : mannitol (1:1) complex.

**Nath et al (2000)** have prepared meloxicam β- cyclodextrin inclusion complexes by using a 23 factorial design experiment by added concentration of PVP (1 to 25% w/v) drug: β-cyclodextrin molar ratio (1:1, 1:2) and autoclaving at 121º for 30 minutes. The complexes were prepared by solvent evaporation method. The 1:2 molar ratio of drug : β-cyclodextrin containing 0.25% w/v PVP showed optimum enhanced solubility both in acid and alkali. The *in vitro* release of tablet meloxicam: β-cyclodextrin complexes showed higher release in both acidic and alkali (77% - pH 1.2 and 93% - pH 7.4) as compared to marketed tablet (38% and acid 1.2 pH).

**Parikh et al (2005)** have prepared nimesulide inclusion complexes with β-cyclodextrin by kneading method and salt with L-arginine and L-lysine by solvent evaporation method. The complexes of nimesulide β-cyclodextrin and salt with L-arginine and L-lycine showed significant increase in the dissolution of the drug as compared to pure drug. There is an appreciable increase in the dissolution in 1:2 nimesulide-β-cyclodextrin ratio.
Saha et al (2002) have prepared inclusion complexes of nimesulide with β-cyclodextrin by solvent evaporation method and solid dispersion of nimesulide and ibuprofen by using various hydrophilic excipient (PEG-6000, sorbitol, PVPK-30, MCC). Solid dispersion of nimesulide with PEG-6000 enhanced the solubility of nimesulide more than 1000%. The dispersion of ibuprofen in sorbitol showed maximum enhancement of solubility up to 75%. The inclusion complexes of nimesulide in β-cyclodextrin also increase the solubility by 663%.

Sanjula et al (2005) have prepared inclusion complexes of rofecoxib by using dimethyl β-cyclodextrin. Complexes were prepared by physical, kneading and spray drying methods. The release profile of the drug from complexes were studied in pH 1.2 and pH 7.4 and it was found that the marketed preparations showed lesser release characteristic as compared to the complex prepared by kneading method.

Sanoferjan et al (2000) have prepared inclusion complexes of tenoxicam with β-cyclodextrin in 1:1M ratio by different methods (neutralization, common solvent, kneading). The complex prepared by neutralization method show best thermal stability, photostability and release rate as compared to common solvents and kneading method.

Soniwala et al (2005) tried to improve the solubility and dissolution rate of a poorly aqueous soluble drug Rofecoxib. They formulated a solid dispersion of Rofecoxib with various hydrophilic carriers like polyethylene glycol 6000, polyvinyl pyrrolidone K-30, eudragit E-100 and also inclusion complex with β cyclodextrin. When drug release profile was studied, it was found out that polyvinylpyrrolidone K-30 was found to be more effective in enhancing the drug dissolution, when compared with polyethylene glycol and eudragit E-100. For further enhancement of dissolution rate, the combination of two dissolution enhancing agent ie polyvinylpyrrolidone K-30 and β Cyclodextrin were used.

Sradhanjali et al (2005) investigated the possibility of enhancement of dissolution rate of a poorly soluble drug, Roxithromycin. They prepared solid dispersions of Roxithromycin using hydrophilic polymers like polyethylene glycol 6000, hydroxypropylmethylcellulose K4M and hydroxypropylcellulose in various ratios. Solid dispersions of Roxithromycin were reported to show an enhancement in dissolution rate compared to pure drug. All solid
dispersions formulated were fine with good flow properties. The solid dispersion formulated using polyethylene glycol 6000 was found to show the highest dissolution efficiency.

Ubaidulla et al (2005) studied about aiming at enhancement of solubility and dissolution of Nimesulide by applying solid dispersion technique followed by formulating it as suspension. The suspensions were characterized by studying particle size and sedimentation volume. In vitro evolution was carried out in USP XXI dissolution apparatus. Nimesulide suspensions with solid dispersion exhibited good suspendability and gave higher dissolution rate than those with plain Nimesulide suspension.

Venkates et al (2005) studied the comparison of dissolution profiles of pure Nalidixic acid, solid dispersion of Nalidixic acid with polyethylene glycol 6000 (PEG 6000) and solid dispersion of Nalidixic acid with polyethylene glycol 6000 incorporated with sodium lauryl sulphate. The comparison studies revealed that solid dispersion prepared using PEG 6000 and sodium laurylsulphate (1% w/w) showed almost instant and complete dissolution than pure drug and dispersions without surfactant. A significant decrease in crystallinity of drug in solid dispersion was suggested to be the mechanism for the increase in dissolution rate. This suggestion was supported by x-ray diffraction studies.

2.2 PAST WORK ON MOUTH DISSOLVING TABLETS:

Koizumi et al (1997) prepared Rapidly Disintegrating Tablet as the oral dosage form for pediatric and geriatric patients. They prepared this type of tablet by forming highly porous, rapidly saliva soluble compressed tablets using a principle of sublimation. In this method, the addition of a volatile salt to tableting components, mixing the components to obtain a substantially homogenous mixture and volatilization the volatile salt, which causes pores on the tablet. The volatile material used was camphor and the diluent used was mannitol and prepared highly porous compressed tablets. The tablet was subjected to vacuum at 80°C for 30 minutes to eliminate camphor and thus creates pores in the tablet, which help in achieving rapid disintegration when the tablet come in contact with saliva within 20 seconds and have sufficient hardness also.
Roser et al (1998) described a method of preparing highly porous and rapidly dissolving tablets, which includes the addition of a sublime salt to the tabletting components, compressing the blend and removing the salt by the process of sublimation. The active ingredient, a diluent (e.g., Lactose and trehalose) a sublime salt (e.g., Ammonium bicarbonate, Ammonium carbonate, and ammonium acetate), a binder and other and other excipients are blended and tablets are prepared. Then volatile salt is removed by sublimation, by exposing the tablet to reduced atmospheric pressure for a time sufficient to completely remove the salt.

Khodadadeh et al (1998) study of the effect of cyproheptadine on gait in hemiplegic children in this study they investigate whether gait function, as specified by stride length, cadence, heart rate, and also by questionnaire, correlated with cyproheptadine medication and found that neither qualitative nor quantitative analyses suggested any systematic change in gait parameters dependent on cyproheptadine medication and also found in the case of mean patient heart rate, which was 10% higher (P<0.003) at the end of the cyproheptadine medication period and conclude that no statistical evidence of improvement in spasticity due to the action of cyproheptadine.

Ashtamkar et al (2003) prepared fast dissolving tablets of Nabumetone using wet granulation method with diluents like lactose, starch, and MCC, binder like starch paste 10%, CMC in water 10% and PVP in alcohol 10% and superdisintegration like sodium starch glycollate, croscarmellose sodium, and crospovidone. The granules and tablets prepared were studied for granule yield, particle size distribution, cars index hardness of granules, tensile strength of tablets In-vitro disintegration time and In vitro release studies by dissolution test In-vitro release profile studies dissolution test. In-vitro release profile were compared with marketed Nabumetone tablets.

Mahajan et al (2004) prepared mouth dissolving tablets of Sumatriptan Succinate using disintegrants sodium starch glycollate, carboxymethyl cellulose sodium and treaded agar by direct compression method. The prepared tablets were evaluated for thickness, uniformity of weight, content uniformity, hardness, tensile strength, porosity, friability, wetting time, water absorption ratio, in vitro disintegration time and in vitro drug release. The tablets
disintegrated \textit{in vitro} and \textit{in vivo} within 10-16 seconds and 12-18 seconds respectively. Almost 90\% of drug was released from all formulation within 10 minute. The formulation containing combination of sodium starch glycollate and carboxy methyl cellulose was found to give best results. The tablet apart from fulfilling all official and other specification, exhibits higher rate of drug release.

\textbf{Kaushik et al (2010)} carried out the formulation and evaluation of mouth dissolving tablet by effervescent formulation approaches. Addition of an effervescent system in the formulation is one of the approaches by which mouth dissolving tablet can be prepared, which have the advantage of easiness to implement, masking of bitter taste of drug and aids in rapid disintergration of tablet in oral cavity. In the study sodium bi-carbonate and citric acid in the olanazapine mouth dissolving tablet give a soothing fizz, excellent mouth feel, good palatability and quick dissolution profile.

\textbf{Panda et al (2004)} carried out the formulation and evaluation of Nimesulide Mouth Dissolving Effervescent Tablets. Here six formulation were prepared each tablet weighting 250mg employing acid (citric acid and tartaric acid in 1:2 ratio) and base (sodium bicarbonate) in the proportion of 15:30:55 by wet granulation method. The tablets were evaluated for drug content and other physical properties and mouth feel. Among the formulations (F2) which contain 15\% of effervescent ingredients divided as internal disintegrants and external ingredients in the ratio of 2:1 found to be best acceptable in term of palatability, fast dissolving, having adequate strength. The disintegration time was found to be 15±2 seconds and hardness 2±0.4kg/cm². Thus concluded that it is possible to prepare mouth fast dissolving tablets employing simple ingredients and conventional method at lower cost.

\textbf{Simone et al (2006)} prepared fast dispersible tablet of ibuprofen by direct compression method. The tablet were prepared by addition of galactomannan and crospovidone. These tablets disperse in water within 40 s and show a crushing strength of 95 N the tablets were evaluated on parameters like wetting time, in-vitro disintegration, mouth feel, in-vitro dissolution studies and stability studies. Special emphasis was paid
to the development of a wetting test, replacing the normal disintegration method. And found dispersible tablets with acceptable hardness and desirable taste could be prepared within the optimum region.

**Yoshio et al (2007)** prepared orally disintegrating (OD) tablets manufactured by compressing a mixture of high melting point sugar alcohol (HMP-SA) and low melting point sugar alcohol (LMP-SA) and subsequent heating. By direct compression method (DCM) and wet granule compression method with added as an aqueous binder solution, the tablets became harder with less heating compared to tablets prepared by DCM compared to mechanically mixed LMP-SA in DCM, resulted that an increase in tablet hardness even with a short heating time and low content of LMP-SA.

**Shailesh et al (2008)** reviewed on fast dissolving tablet and described requirements, advantages and conventional techniques are used for preparation of fast dissolving drug delivery system i.e. Freeze drying, moulding, sublimation, spray-drying, mass-extrusion, direct compression and various patented technologies for fast dissolving tablets, he also described the list of drugs to be promising in corporate in fast dissolving tablets.

**Yoshio et al (2008)** prepared orally disintegrating (OD) tablets manufactured by phase transition of sugar alcohol. OD tablets were produced by directly compressing a mixture containing lactose–xylitol granules, disintegrant, glidant and lubricant, and subsequent heating with different lubricants and studied the effect of the type of lubricant on the tablet characteristics was evaluated using magnesium stearate (Mg-St), sodium stearyl fumarate (SSF), and talc as lubricants. found that oral disintegration time of the tablets containing talc was not changed despite of an increase in hardness. The water absorption rate of the tablets containing talc was much faster than that of the tablets containing other lubricants.

**Ravi et al (2010)** prepared mouth dissolving Tablets of aceclofenac by effervescent formulation approach with sodium bicarbonate, tartaric acid, sodium glycine carbonate and citric acid and found that 10:8 ratio of heat treated sodium bicarbonate and citric acid in the aceclofenac mouth dissolving tablets gave a soothing fizz, excellent mouth feel, good
palatability and quick dissolution profile and stable during the stability studies conducted as per ICH guidelines, as it showed no significant changes ($P<0.05$) in the physicochemical properties, disintegration time and in vitro drug release.

**Rakesh et al (2010)** prepared dispersible tablet of cefditoren pivoxil by wet granulation method by using different superdisintegrant croscarmellose sodium (CCS), sodium starch glycolate (SSG) and crospovidone were evaluated for weight variation, content uniformity, hardness, disintegration time, and friability of tablets. And found that 8:2 in whole experiment as it gives minimum disintegration time.

**Rakesh Pahwa et al, (2010)** reviewed that Orally Disintegrating Tablets - Friendly to Pediatrics and Geriatrics and described Significance, characteristics, manufacture methods, patented technologies of ODTs. found that ODTs can be prepared in several ways and product performance depends upon the drug suitability and excipients selection in the delivery system. and conclude that ODTs offer numerous significant advantages over conventional dosage forms because of improved efficacy, bioavailability, rapid onset of action, better patient compliance and acceptance.

**Kalpesh et al (2011)** prepared Fast Disintegrating Tablet of Aceclofenac by Sublimation Method the tablet were prepared by addition of crospovidone and sodium starch glycolate with camphor. The prepared batches of tablets were evaluated for thickness, weigh variation, hardness, friability, drug content uniformity, wetting time, water absorption ratio, in vitro disintegration time and in-vitro drug release. Formulations were tested for the in-vitro drug release pattern (in pH 7.4 phosphate buffer) and found that the formulation prepared by using 8% w/w of crospovidone and emerged as the overall best formulation based on the in vitro drug release characteristics.