2. Literature review

2.1 Literature review on rapidly dissolving films

Cilurzo et al (1) studied maltodextrins with a low dextrose equivalent as a film forming material and its application in the design of fast dissolving films of piroxicam. The effect of plasticizer concentration was studied on the mechanical property of the film. Flexible films were obtained by using 16-20 % w/w glycerin. Casting, solvent evaporation and hot melt extrusion were used as production technologies by adding sorbitan monooleate and microcrystalline cellulose respectively. It was observed that microcrystalline cellulose decreased film ductility and affected in-vitro and in-vivo film disintegration. The films exhibited a high loading capacity up to 25 mg per 6 cm² of surface. The dissolution rate of piroxicam was significantly improved in films prepared by casting and solvent evaporation independently of piroxicam to maltodextrin ratio.

Dinge et al (2) investigated formulation of triclosan (TC) containing fast dissolving films for local delivery to oral cavity. Various film forming agents, film modifiers and polyhydric alcohols were evaluated for optimizing the composition of fast dissolving films. The potential of poloxamer 407 and hydroxypropyl-beta- cyclodextrin (HPBCD) to improve solubility of TC was investigated. Fast dissolving films containing hydroxypropyl methylcellulose (HPMC), xanthan gum, and xylitol were formulated. Use of poloxamer 407 and HPBCD resulted in significant improvement in the solubility of TC. Films containing TC-poloxamer 407 exhibited better in vitro dissolution profile and in vitro antimicrobial activity as compared to films containing TC-HPBCD complex.

Chen et al (3) investigated fast dissolving and extended release edible films for dissolution time, release profiles and film strength. Benzocaine, caffeine, lidocaine and diphenhydramine were used as a model drugs. Various film forming polymers were employed in the study namely hydroxypropyl methylcellulose, methylcellulose and polyethylene oxide. The disintegration and dissolution time of the films reflected the fast
dissolving and extended release applications which depended on the nature of film forming polymers. Four different systems were prepared and evaluated. The first and second systems were edible films containing polymers, plasticizers, benzocaine or caffeine along with other excipients. Third system was a buccal film delivery system. Fourth system included cold pack and wound dressing products. As the film thickness increased, the disintegration and dissolution time increased. However, at same thickness, higher loading of the API decreased the disintegration and dissolution time of the films. The puncture strength of HPMC E series increased when molecular weight of the polymer increased. The mechanical strength of polyox (PEO) films also showed similar observations. The puncture strength of PEO is much lower than that of cellulose based methyl cellulose and HPMC polymers.

Mashru et al (4) prepared fast dissolving films for sublingual route containing salbutamol sulphate and polyvinyl alcohol as polymer. The films were evaluated for mechanical properties, in vitro release study and morphology study. A $3^3$ factorial design was applied to study the effect of polyvinyl alcohol, glycerin and mannitol on % drug release and mechanical properties of the films. It was observed that polyvinyl alcohol had positive effect on tensile strength and mannitol had negative effect on tensile strength. Mannitol produced positive effect on drug release where as polyvinyl alcohol produced negative effect on drug release.

Ali S and Anisul Q (5) examined high molecular weight povidone K-90 polymer as a film forming excipient for fast dissolving drug delivery applications. It was evaluated in combination with povidone K-30 and other kollidon SR polymers. Fast dissolving films suitable for delivery of highly potent drugs and vitamins could be formulated using the polymer povidone K 90 with auxiliary polymers. K-90 films with increased amount of polyvinyl acetate and acrylic acid based kollidon SR and MAE 100P respectively showed significant flexibility and elongation. Increased amount of K-30 and kollidon VA 64 showed good flexibility. All films were highly hydrophilic and dissolved in 60 s or less except K90/kollicoat MAE 100P which dissolves in 6-7 min.
2. Literature review

Onishi et al (6) developed novel mucoadhesive patch of diazepam to achieve its rapid absorption for the emergency treatment of epileptic seizure or anxiety disorder. The patch consisted of outer mucoadhesive region of carbopol 934, central drug region and tegaderm as backing layer. Diazepam was dissolved in propylene glycol alone or propylene glycol containing oleic acid at 5.6%w/w.

Chen et al (7) formulated fast dissolving films using water soluble polymers for achieving rapid disintegration, good mouth feel and mechanical properties. Desired fast disintegration and mechanical properties could be tailored with polyethylene oxide and HPMC. Films had good mouth feel and no sticky feeling. Film strength of films containing PEO and HPMC ranged between 3000 kg/m² to 17000 kg/m². Increase in glycerin content resulted in marked decrease in film strength.

Cilurzo F et al (8) developed fast dissolving film containing maltodextrin using hot melt extrusion technology. The loading capacity and in-vivo performance of the film were assayed by using paracetamol as model drug. The film contained glucidex, glycerin, paracetamol, avicel pH101 and menthol. The thickness of the film was 317± 3 µm. The maximum load was 12.2 N and elongation at break was 5.9 mm.

Honary et al (9) studied effect of different molecular weights and concentration of PEG as plasticizer in HPMC films. Thermomechanical and mechanical properties of the cast films were tested using tensile and dynamic mechanical thermal analysis testing. Addition of plasticizer decreased both properties. Lower grades of PEG i.e. 300, 400 and 600 had more effect than higher molecular weights and concentrations. Glass transition temperature (Tg) decreased as molecular weight of PEG decreased and this effect was more pronounced for lower molecular weight than higher molecular weight PEG. Effect of molecular weight was much higher than effect of concentration of PEG.

World Patent WO/2008/040534 disclosed an invention by Leichs et al (10) containing mucoadhesive orally disintegrating film for delivering active pharmaceutical agents (API) such as donepezil, ondansetron (0.05-50%w/w of total weight of formulation).
These films disintegrated upon contact with saliva in buccal cavity in 60 sec. The film was bioequivalent to immediate release or orally disintegrating tablets containing same amount of API.

**World patent WO/2005/048980** (11) described orally consumable film composition comprising a mixture of starch and alginate at a ratio 1: 2.5 to 1:4, antimicrobial agents such as menthol, eucalyptol and methyl salicylate, plasticizer, filler like MCC, stabilizing agent and sweetening agent. Films prepared had excellent tensile strength and % elongation. Alginate alone produced film with high tensile strength but low elongation. Starch alone produced good elongation but low strength and was poorly detachable. Preferable ratio was 1:3 to 1:3.5 and % of plasticizer was 1-5% by weight. MCC was used in concentration 0.1-1% of total weight of film composition.

**Ivory et al (12)** formulated rapidly dissolving edible films with cellulose film forming polymers which includes one as high viscosity like HPMC K4M, K100, K3, E50 and E4M and one as low viscosity polymer grade like methyl cellulose, carboxymethyl cellulose, hydroxyethyl cellulose, hydroxyl propyl cellulose and hydroxyl propyl methyl cellulose. Active pharmaceutical agents include categories of anti-inflammatory, H2-antagonists, vitamins, nutritional supplements, desensitizing agents, sedative, hypnotics, antibiotics, anti-tussives, anti-histamines, decongestants, expectorants etc. The formula also includes plasticizer and flavour. The amount of plasticizer present was 2-5% by weight of dry film composition.

World patent WO/2004/096193 by **Fadden et al (13)** indicates formulation of fast dissolving films containing pregelatinized modified starch for improved heat and moisture resistance and water soluble polymer pullulan containing pharmaceutically active agents like dextromethorphan. Amberlite IRP 69 was used for taste masking of the drug.
US Patent 20040180077 by Riker D et al (14) describes composition of rapidly dissolving films for treating obesity. The active agents included are caffeine, tea extract, theobromine and ginseng. Modified corn starch was used as the film forming polymer. Plasticizers like propylene glycol and polysorbate 80 were used at 1% concentration in the formulation. The film comprises 100 mg caffeine. Typical strips were 1-5 mm thick, 10-50 wide, 10-50 mm long and 20-100 mg in weight.

Yasuda et al (15) prepared quickly soluble film preparations as disclosed in US Patent 20050147653, containing one drug containing layer and a support layer on one or both sides containing HPMC and HPC. The film was evaluated for mechanical properties and water disintegration test. The compounding ratio of drug was 0.01 to 40 % by wt and 40-99.99% by wt polymer. The disintegration time was less than 300 sec. The tensile strength was 200-3000 g/15 min.

Rapidly dissolvable breath freshening films containing HPMC and water dispersible starch (pregelatinized starch) and flavoring agents were formulated and disclosed in World patent WO/2003/015749 by Xu et al (16). HPMC E5 to starch was taken in ratio 1: 1.5 to 2: 5.1. HPMC provides mechanical strength and maintains integrity of the film at elevated temperature. Starch increases stiffness of the film and reduces curling of the film. The thickness of the film was 41µm and disintegration time was 30 sec.

Chen et al (17) disclosed dosage forms of mono or bilayer of nicotine delivery system in the form of mucoadhesive film in US Patent 200300683776, made of one or more non-microbial hydrocolloids including HPMC, HPC, methyl cellulose and ethyl cellulose. At least 50% of nicotine is present in neutral form in the formulation. The disintegration time was between 1-300 sec and dissolution time was 0.5-5 min.

A composition containing therapeutic and/or breath freshening agents for use in the oral cavity is disclosed in US Patent 20020150544 by Zerbe et al (18). It consists of water soluble polymers like HPMC, HEC and HPC in combination with ingredients and provides therapeutic and/or cosmetic effect. The film is coated and dried utilizing
existing coating technology and exhibits instant wettability followed by rapid disintegration in the oral cavity. 50-75% of water soluble polymer is present in dry film. It also contains plasticizer like glycerin, PEG, propylene glycol and surfactants (0.1-5%w/w).

World patent WO/2001/070194 disclosed by Bess et al (19) involved fast dissolving orally consumable films containing pullulan (40-80% weight of the film), ion exchange resin Amberlite IRP 69 for taste masking of dextromethorphan. The drug was present in 5-40% by weight of the film, amount of Amberlite IRP 69 present is 5-40% weight of the film. The optimized ratio of drug to resin is 1:3 to 3:1 preferably in the ratio 1:1. The active film had pleasing appearance and taste.

World patent WO/2004/096192 by Kulkarni et al (20) shows formulation of fast dissolving orally consumable films containing pullulan, pharmaceutically active agent, essential oil (like thymol, menthol, eucalyptol and methyl salicylate) and sweetener sucralose. The pharmaceutically active agent included is dextromethorphan hydrobromide along with ion exchange resin Amberlite resin IRP 69. The ratio of dextromethophan : Amberlite IRP 69 is 1:1.

US Patent 20070092564 by Li et al (21) concerns with orally disintegrating formulation containing pullulan, amino acid glycine, thickening and suspending agents. Lyophilization was used as a technique for solid formulation. Examples of drugs include rotundine, breviscapine, loratidine and itopride HCl. Ratio of amino acid to pullulan is 0.5:1.5.
2.2 Literature review on rapidly dissolving dosage forms

Purvis et al (22) prepared rapidly dissolving formulations of the poorly water-soluble drug repaglinide using ultra-rapid freezing technique (URF), and investigated the influence of type of excipients on repaglinide stability. Repaglinide compositions containing different types and levels of excipients and different drug potencies (50%-86%) were produced by the URF technology. Surfactants, including sodium dodecyl sulfate, and alkalizing agents such as diethanolamine (DEA) and tromethamine (TRIS) were incorporated into the compositions. Forced degradation of repaglinide was conducted under stressed conditions (e.g., elevated temperature, exposure to peroxide) to determine the stability of the drug in such environments. It was concluded that the solubility of repaglinide increased as a function of increasing pH; therefore, incorporation of an alkalizing agent into the URF formulations increased the drug’s solubility. Drug instability resulted when the drug was exposed to pH values above 9. URF formulations containing alkalizing agents showed no degradation or spontaneous recrystallization in the formulation, indicating that increased stability was achieved by processing.

Ciper et al (23) prepared novel capsule-based fast disintegrating dosage forms for the oral cavity (Fastcaps). Films were casted from various additive-containing gelatin solutions and evaluated with respect to disintegration time and mechanical properties so as to identify suitable formulations for the capsule preparation. The disintegration time of films decreased with decreasing bloom strength and could be further decreased by the addition of sugars or PEGs. Fast disintegrating capsules were successfully prepared by a dipping process, where parameters such as the viscosity and temperature of the dipping solution and the dipping velocity of the steel pins were optimized. The required viscosity range of the dipping solution for Fastcap manufacturing was 500–600 cP. The addition of the hydrophilic additives (xylitol, sorbitol or PEG 1500) did not significantly affect the viscosity and gelation temperature of the dipping solution. The in vitro disintegration of Fastcaps (30–45 sec) was twice as rapid as the one of regular hard gelatin capsules. In vivo, Fastcaps disintegrated rapidly (9–13 sec) and their content was spread throughout
the oral cavity within seconds. Lactose and/or microcrystalline cellulose were suitable fillers for Fastcaps.

**Ciper et al (24)** prepared fast disintegrating capsules for administration in the oral cavity either by perforation or by vacuum-drying of conventional hard capsules. When compared to other fast disintegrating dosage forms (e.g. lyophilized sponges or tablets), these capsules exhibited various advantages, in particular, a high drug loading capacity and no compression steps. The disintegration time of conventional hard gelatin capsules (HGC) was reduced from 91 to 39 sec by introducing 6-10 small holes (diameter =25-50 micron) into the capsule shell. Vacuum-drying of conventional hard gelatin capsules resulted in brittle capsules, which broke rapidly in the oral cavity. The brittleness of the hard gelatin capsules correlated well with their moisture content. The critical moisture value for sufficient brittleness of hard gelatin capsules was <4% w/w. In contrast, HPMC capsules remained flexible, even at low moisture content. The moisture uptake of various capsule fillers was in the order of Avicel PH101 > lactose > Avicel PH112 > mannitol.

**Ahmed et al (25)** studied the pharmacokinetics of ketoprofen from a fast-dissolving lyophilized tablet (LT), as compared to an immediate release (IR) tablet as reference after single oral dose (25 mg) administration in six healthy subjects aged between 25-40 years using a randomized crossover design. The rate of absorption of ketoprofen from LT was significantly faster than that of IR tablet and had significantly higher C\text{max} (by about 50%) and earlier t\text{max} (by 15 min), whereas the extent of absorption expressed by AUC was about 68% higher as compared to the IR tablet. The relative bioavailability (f \text{rel}) of the LT compared with the IR tablet was 168%. The difference between the two formulations for half-life and MRT were statistically significant (p<0.05). Ketoprofen LT remained physically and chemically stable for 12 months at 25 °C and 60% relative humidity.

**Van Schaick et al (26)** evaluated the bioequivalence of a fast-disintegrating oral tablet of risperidone with conventional oral tablet. A randomized, open-label, 2-way crossover trial was taken in which healthy volunteers received two 0.5-mg tablets of a fast-disintegrating oral risperidone formulation and two 0.5-mg tablets of conventional oral risperidone, each in a single administration. The plasma concentration-time profiles of
the active moiety, risperidone, and 9-hydroxy-risperidone were similar after intake of the 2 formulations. The fast-disintegrating tablet and the conventional tablet showed bioequivalence with respect to the active moiety, risperidone, and 9-hydroxy-risperidone. A single administration of two 0.5-mg fast-disintegrating risperidone tablets was bioequivalent to a single administration of two 0.5-mg conventional risperidone tablets.

Mishra et al (27) studied the suitability of spray dried excipient base in the formulation of orally disintegrating tablet containing Valdecoxib (low aqueous solubility drug) and Metoclopramide (high aqueous solubility drug). Spray dried excipient base was prepared using Scientech spray drier. Super disintegrants (such as Ac-Di-Sol, Kollidon CL, sodium starch glycolate), diluent (mannitol) along with sweetening agent (aspartame) were used in the formulation of tablets. The tablets were evaluated for hardness, friability, water absorption ratio, disintegration time and in vitro drug release. Using the same excipients, the tablets were prepared by direct compression and evaluated. Maximum drug release and minimum disintegration time were observed with Kollidon CL excipient base as compared to tablets prepared by direct compression, showing the superiority of the spray dried excipient base technique over direct compression technique.

Amin et al (28) formulated orally disintegrating tablets (ODTs) of etoricoxib. Tablets were prepared using direct compression method employing superdisintegrants such as low substituted hydroxylpropyl methyl cellulose, low substituted hydroxyl-propyl cellulose, crospovidone, croscarmellose sodium, and sodium starch glycolate. Tablets of etoricoxib prepared using L-HPC exhibited the least friability and disintegration time (approximately 65 sec). Sublimation technique was used in the preparation of ODTs. The addition of camphor lowered the disintegration time (to 30 sec), but the percent friability was increased. A $3^2$ full factorial design was employed to study the joint influence of the amount of superdisintegrant (L-HPC) and the amount of sublimating agent (camphor) on the percent of friability and the disintegration time. The results of multiple linear regression analysis revealed that for obtaining an effective ODT of etoricoxib, higher percentages of L-HPC and camphor should be used.
Gohel et al (29) developed mouth dissolve tablets of nimesulide. Granules containing nimesulide, camphor and crospovidone were prepared by wet granulation technique. Camphor was sublimed from the dried granules by exposure to vacuum. The tablets were evaluated for friability, wetting time, and disintegration time. A $3^2$ full factorial design was used to investigate the joint influence of amount of camphor and crospovidone. The results of multiple linear regression analysis revealed that for obtaining a rapidly disintegrating dosage form, tablets should be prepared using an optimum concentration of camphor and a higher percentage of crospovidone. Sublimation of camphor from tablets resulted in superior tablets as compared with the tablets prepared from granules exposed earlier to vacuum.

Singh et al (30) optimized an orodispersible formulation of indomethacin using a combined approach of subliming agent and superdisintegrant. The tablets were made by non-aqueous wet granulation technique with superdisintegrant used intragranularly and extragranularly. A $2^3$ factorial design was used to investigate the effects of amount of subliming agents namely camphor and ammonium bicarbonate and taste masking and sootherning hydrophilic agent mannitol as independent variables and disintegration time and crushing strength as dependent responses. Optimized orodispersible tablets were evaluated for wetting time, water absorption ratio, porosity and in vitro and in vivo disintegration tests. Results show that higher levels of camphor and mannitol and a lower level of ammonium bicarbonate are desirable for orodispersion.

Gafitanu et al (31) prepared and studied release characteristics of the tablets of propiphenazone made by lyophilization method (lyoc) and compared them with the tablets obtained by simple compression. Propiphenazone, is a stable drug with poor solubility. Method of paste preparation was chosen to prepare the lyoc tablets. These tablets had spongy feel, with a desegregation time of 1-2 min. The conventional tablets had desegregation time of about 9 min. The relative bioavailability for these two types of tablets exhibited the differences, confirming the evident advantages in use of lyoc tablets in analgesic and antipyretic therapy.
Ahmed et al (32) developed a ketoprofen tablet which dissolves rapidly in the mouth, therefore, needing not be swallowed. The solubility and dissolution rate of poorly water-soluble ketoprofen was improved by preparing a lyophilized tablet (LT) of ketoprofen using freeze-drying technique. The LT was prepared by dispersing the drug in an aqueous solution of highly water-soluble carrier materials consisting of gelatin, glycine, and sorbitol. The mixture was dosed into the pockets of blister packs and then was subjected to lyophilization. The saturation solubility and dissolution characteristics of ketoprofen from the LT were investigated and compared with pure drug and the physical mixture. Results showed that increase in solubility of ketoprofen from LT matrix was nearly three times greater than the solubility of the pure drug, which was attributed to supersaturation generated by amorphous form of the drug. Dissolution studies showed that LT of ketoprofen significantly improved the dissolution rate of the drug compared with the physical mixture and pure drug. More than 95% of ketoprofen in LT was dissolved within 5 min compared to only 45% of ketoprofen dissolved during 60 min.

Chandrasekhar et al (33) optimized fast disintegrating tablets (FDTs) using a progressive three-stage approach. A series of hardness, fracturability and disintegration time tests were measured on the formulations at each stage. During Stage I, tablets were prepared in concentrations between 2% and 5% w/w, and were formulated at each concentration as single and combination bloom strength gelatin (BSG) using 75 and 225 BSGs. Analysis revealed that both hardness and disintegration time increased with an increase in gelatin concentration. A combination (5% gelatin) FDT comprising a 50:50 ratio of 75:225 BSGs (hardness: 13.7+/−0.9 N and disintegration time: 24.1+/−0.6 s) was judged the most ideal, and was carried forward to Stage II where the addition of the saccharides sorbitol, mannitol and sucrose in concentrations between 10% and 80% w/w was done. The best properties were exhibited by mannitol-containing formulations (50%-hardness: 30.9+/−2.8 N and disintegration time: 13.3+/−2.1 sec), which were carried forward to stage III. The viscosity-modifying polymers were added to improve mouth-feel and aid pre-gastric retention. Addition of carbopol 974P-NF resulted in the enhancement of viscosity with a compromise of the hardness of the tablet, whereas Pluronic F127 (6%) showed an increase in disintegration time and viscosity with retention of mechanical properties.
Ahmed et al (34) developed a fast-disintegrating lyophilized dry emulsion (LDE) tablet that enhanced the in vitro dissolution and in vivo absorption of griseofulvin (GF). The LDE tablets were prepared by freeze-drying o/w emulsions of GF, a drug for which bioavailability is known to be enhanced by fat co-administration. Oil-in-water emulsions were prepared using a gelatin solution (2%, w/v) as the water phase and medium chain triglycerides (Miglyol) or sesame oil as the oil phase. A significant influence of the emulsifier type was seen on the tablet disintegration time (p<0.01). Results obtained from dissolution studies showed that LDE tablets of GF improved the dissolution rate of the drug compared to the plain drug. The rate of absorption of GF from LDE tablet was faster than that from the reference tablet and had significantly higher (p=0.02) peak plasma concentration (more than three times higher) and shortened time to C_max by 4 h (p=0.014). The extent of absorption expressed by AUC was 85% larger as compared to the commercial tablet.

Jacob et al (35) developed fast-dissolving effervescent tablets (FETs) by the modification of non-reactive liquid-based wet granulation technique. Main objective was to develop FETs of glibenclamide based on highly plastic granules that can be compressed at low pressure to form fast-melting tablets. In this study, screening of various acid and carbonate sources for the effervescent system was done. e.g. citric acid was coated with plastic materials such as polyethylene glycol (PEG), sodium bicarbonate was blended with sugar alcohol like mannitol, which would give a protective coating and PEG 1000 which melts at body temperature. The optimized formulation using citric acid-sodium bicarbonate and citric acid-sodium glycine carbonate tablet with PEG and mannitol was found to have better reaction properties and reaction stability than does the standard citric acid-sodium bicarbonate tablet. FETs of glibenclamide might aid in dissolution due to increase in microenvironmental pH around the granules and saliva.

Goel et al (36) optimized the formulation of fast disintegrating tablets (FDTs) for nausea and vomiting using aminoacetic acid, carmellose and sodium alginate with enough mechanical strength. Ondansetron HCl (water soluble) or domperidone (water insoluble) drug were added to FDTs and their disintegration behaviour was evaluated. Plackett Burman Screening Design was used to screen the independent active process variables.
concentration of aminoacetic acid $X_1$, concentration of carmellose $X_2$ and tablet crushing strength $X_3$ which were found to actively influence the dependent variables disintegration time in the mouth (DT), wetting time (WT), and water absorption ratio (WAR) for both the drugs. FDTs containing domperidone was prepared according to central composite design for estimating the effect of active factors $X_1$, $X_2$, $X_3$ in extended spherical domain. The regression analysis of quadratic fit revealed that DT, WT and WAR were 98% correlated with active factors $X_1$, $X_2$ or $X_3$. The optimized domperidone FDTs were further compared with superdisintegrants (croskarmellose sodium or crospovidone). The data revealed that optimized domperidone FDTs were better than domperidone FDTs containing croskarmellose or crospovidone.

Ishikawa et al (37) prepared rapidly disintegrating tablets using microcrystalline cellulose (Avicel PH-M series) in the formulation of tablets to decrease the sensation of roughness when a tablet, which is rapidly disintegrated by saliva containing acetaminophen or ascorbic acid as model drugs. Tablets prepared using spherical microcrystalline cellulose, PH-M-06, with the smallest particle size (mean value, 7 µ) had sufficient crushing strength (approximately, 8 kg) and rapidly disintegrated (within 15 sec) when the mixing ratio of PH-M-06 to low-substituted hydroxypropylcellulose (L-HPC) was 9:1. Sensory evaluation by volunteers showed that PH-M-06 was superior to PH-102 in terms of the feeling of roughness in the mouth. Consequently, it was found that particle size is an important factor for tablet preparation using microcrystalline cellulose. Drugs such as acetaminophen and ascorbic acid (concentration of approximately 50%) could be incorporated in the tablet form using PH-NM-06 in combination with L-HPC as a good disintegrant at a low compression force (1-6 kN).

Fukami et al (38) formulated a fast disintegrating compressed tablet using amino acids, such as L-lysine HCl, L-alanine, glycine and L-tyrosine as disintegration accelerator. The tablets having the hardness of about 4 kgf were prepared and the effect of amino acids on the wetting time and disintegration time in the oral cavity of tablets was examined on the basis of surface free energy of amino acids. The wetting time of the tablets increased in the order of L-lysine HCl, L-alanine, glycine and L-tyrosine, whereas the disintegration time in the oral cavity of the tablets increased in the order of L-alanine, glycine, L-lysine.
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HCl and L-tyrosine. The behavior was analyzed by the introduction of surface free energy which revealed that when the polar component of amino acid was large value or the dispersion component was small value, faster wetting of tablet was observed. When the dispersion component of amino acid was large value or the dispersion component was small value, faster disintegration of tablet was observed, expect of L-tyrosine tablet.
2.3 Literature review on taste masking techniques

US Patent US 20070286903 by Becicka et al (39) described taste masked composition of an active pharmaceutical agent loperamide hydrochloride for oral delivery. Taste masked granules of loperamide hydrochloride were prepared by using a premix of dibutyl sebacate, ethyl cellulose dispersion (30%) and PEG 3350. It was followed by addition of loperamide hydrochloride and Amberlite IRP 64 to form homogenous mixture.

An orally disintegrating composition was disclosed by Dharmadhikari et al (40) in US Patent 20060198885. Reduced bitterness of cetirizine was observed using alkaline earth oxide i.e. calcium oxide and magnesium oxide (1-5% by weight of the composition) and pharmaceutically acceptable carrier which comprises disintegrant like sodium starch glycolate and pregelatinized starch (15-40% by weight of the composition). The disintegration time was less than 1 min in the oral cavity.

Santos et al (41) disclosed an invention in US patent 7101572 regarding taste masked aqueous liquid pharmaceutical composition of unpleasant tasting drug dissolved or dispersed in aqueous excipient base of PVP and copovidone and high molecular weight PEG 2000-8000. Various viscosity enhancing agents and sweetening agents were used. pH was between 2.5-8. The % of PVP and copovidone were 1-7%. PEG was used in the concentration 0.1-5%. Unpleasant tasting drug was selected from a group consisting of an analgesic, anti-inflammatory drug, anti-histamine, anti-infective, decongestant, mucolytic, anti-tussive and an expectorant.

A method for preparing orally disintegrating tablet was provided by Lai et al (42) in US Patent 200601050038 comprising microparticles of one or more taste masked drugs (sumatriptan, zolmitriptan, cetirizine, fexofenadine and ondansetron) produced by solvent coacervation with mixture of ethyl cellulose and CaCO₃. Amount of drug released in 30 min is not less than 75% in 900 ml of 0.1 N HCl.
**2. Literature review**

**Chaudhari et al (43)** prepared taste masked solid dosage form i.e. tablet of cetirizine hydrochloride in US Patent 20060083786 by providing coating of film forming water insoluble polymer ethyl cellulose (40-60% of total weight of coating layer) and pH dependent water insoluble polymer which is methacrylic acid copolymer (35-55% of total weight of coating layer) which dissolves at pH below 5. Adsorbent material such as aluminium magnesium silicate was used as coating material.

US Patent 6245353 by **Trithart et al (44)** disclosed a solid, effervescent, rapidly dissolving dosage form for oral administration of cetirizine or a pharmaceutically acceptable salt there of. An effervescent base comprised of at least one of organic edible acid such as citric acid, tartaric acid, a salt there of, at least one of an alkali metal and alkaline earth metal carbonate and bicarbonate i.e. sodium bicarbonate and sodium carbonate. The composition also contained mannitol and pharmatose. The effervescent base for each dose of 50-3000 mg contains 50-2000 mg sodium bicarbonate, 20-200 mg sodium carbonate, 20-1500 mg citric acid and 20-500 mg tartaric acid.

**Fanara et al (45)** disclosed method in US Patent 6455533 for producing oral dosage form i.e. chewable tablet, dry syrup, granules or sublingual tablets comprising beta cyclodextrins and pharmaceutically active agents like cetirizine, hydroxyzine, buclizine, meclizine. The molar ratio of cyclodextrin to cetirizine was 1:4. At the optimized ratio of cyclodextrin to cetirizine, there was absence of bitterness in 7 individuals selected for the taste masking study.

World patent WO/2003/084511 by **Kasraian K et al (46)** describes chewable tablet containing cetirizine, grape and vanilla flavoring agent and beta cyclodextrin. Sweetener used for taste masking was acesulfame-K. Grape and vanilla flavours in the ratio 4:1 to 2:1 were used in the study. The bilayer tablet contains cetirizine hydrochloride 2.22% by weight and 18.33% by weight beta cyclodextrins.

US Patent 20070086974 discloses a method for preparing stable and palatable taste masked chewable tablets of cetirizine hydrochloride by **Gawande et al (47)**. The ion
exchange resin selected was copolymer of methacrylic acid and divinylbenzene. pH of the aqueous solution was 5. Ratio of cetirizine to resin was 1:3 to 1:5. Other excipients included were mannitol, copovidone, MCC and lubricant.

World patent WO/2006/061700 by Antarkar et al (48) disclosed rapidly disintegrating taste masked compositions (granules for dispersion, tablet, dry syrup, base for chewing gum) by forming resinate of cetirizine hydrochloride. The resin used was sulphonated copolymer of styrene and DVB and/or methacrylic acid and DVB. The in-vivo disintegration time was 30-45 sec. The ratio of resin to cetirizine hydrochloride was 1:1 to 2:1.

World patent WO2006/101536 (49) described fast melting tablets with taste masking and sustained release property. Numbers of drugs were taken for the study. Drug resin complex prepared included drugs like dextromethorphan, diphenylhdramine and cetirizine. Amberlite IRP 69 was used for complex formation with dextromethorphan. Amberlite IRP 64 was used in the ratio of 1:2.5 for cetirizine to resin.

Agarwal et al (50) prepared ion exchange resin complex of chloroquine phosphate using polyacrylic acid as ion exchange resin. Taste evaluation of the adsorbates shows significant masking of bitterness of the drug. Complex formation was complete at pH 6. Optimization of resin to drug was at 2:1 ratio. 100% drug release was observed within 5 minutes at pH 1.2.

Kadam et al (51) formulated tasteless complexes of ciprofloxacin with indion 234. The molecular properties of the drug complexes were evaluated. The effect of process, complexation time, temperature and pH on the drug loading was reported. Efficient drug loading was evident in batch process using activated indion 234 with drug: resin ratio of 1:1.3. Drug complexation enhanced with pH from 1.2 to 6. Complete drug release was observed at gastric pH in 2 h.
Shukla et al (52) designed a process to fabricate a tasteless complex of risperidone using ion exchange resin (IER), evaluated the molecular properties of the resinate and incorporated it into orally disintegrating tablets (ODT). The resinate formation using Amberlite IRP64, was confirmed using fourier transform-infrared (FT-IR), X-ray diffraction (XRD) and differential scanning calorimetry (DSC). The maximum loading efficiency achieved was 99.72+/−0.16% in 1:4 (drug : resin weight) ratio at pH 6.0, temperature at 22°C in a period of 1.5 h using ethanol : water (1:1, v/v) as the complexation medium. The complex was compressed into orally disintegrating tablet. The drug release from the complex was about 2.5% in 120 sec in 5 ml of pH 6.8 phosphate buffer which has been used to mimic the salivary fluid volume and pH. Dissolution studies using 500 ml of 0.1 N HCl released 92% in 5 min, indicating complete drug release from the complex in the stomach.

Bhise et al (53) masked the bitter taste of Diphenhydramine Hydrochloride (DPH) using cation exchange resins indion 234 and Tulsion 343 that contained crosslinked polyacrylic backbone. The drug resin complexes (DRC) were prepared by batch process by taking drug: resin ratios 1:1, 1:2, and 1:3. The optimum drug: resin ratio and the time required for maximum complexation was determined. The drug resinates were evaluated for the drug content, taste, micromeritic properties drug release and X-ray diffraction (PXRD). Effervescent and dispersible tablets were developed from optimum drug:resin ratios of 1:2 and 1:1. The X-ray diffraction study confirmed the monomolecularity of entrapped drug in the resin beads. The taste evaluation depicted the successful taste masking of DPH with drug resin complexes. The drug release of 95% in 15 min was observed for effervescent and dispersible tablets.

Shah et al (54) masked the intensely bitter taste of primaquine phosphate (PRM) and formulated its suspension powder (cachets). Taste masking was done using beta-cyclodextrin. 1:25 M physical mixture (CD) was selected based on bitterness score. Cachets were evaluated for angle of repose, sedimentation characterization and pH. In vitro drug release studies for physical mixture and kneaded system were performed at pH 1.2 and 6.8. Bitterness score was evaluated using gustatory sensation test. Phase solubility studies showed weak interaction between PRM and CD. The FTIR, DSC and
XRPD studies indicated inclusion complexation in physical mixture and kneaded system. Kneaded system and physical mixture exhibited better drug release at pH 1.2 and negligible effect at pH 6.8. Cachets prepared using physical mixture showed complete bitter taste masking and easy redispersibility.

Patel et al (55) evaluated the potential of ternary complexation (comprising of drug, cyclodextrin and polymer) as an approach for taste masking. Famotidine with property of bitter taste was selected as a model drug. Improvement in taste masking was evaluated by formulating a ternary complex including hydrophilic polymer hydroxyl propyl methyl cellulose (HPMC 5 cps) as the third component. Phase solubility analysis at 25°C was carried out for both the binary systems (viz. drug-cyclodextrin and drug-polymer) and the ternary system (drug-cyclodextrin-polymer). Ternary complex was prepared using solution method and was further characterized using XRD, DSC, FTIR and microscopic studies. Results obtained from phase solubility analysis showed that the combined use of polymer and cyclodextrin effectively increased the stability constant of the complex. Ternary system showed effective taste masking as compared to binary complex and at the same time showed no limiting effect on the drug release (D.E(15min) = 90%).

Khan et al (56) masked the intensely bitter taste of Ondansetron HCl and formulated its rapid-disintegrating tablet (RDT). Taste masking was done by complexing ondansetron HCl with aminoalkyl methacrylate copolymer (Eudragit EPO) in different ratios by the precipitation method. Drug-polymer complexes (DPCs) were tested for drug content, in vitro taste in simulated salivary fluid (SSF) of pH 6.2, and molecular property. Polyplasdone XL-10 7% wt/wt gave the minimum disintegration time. Tablets containing spray-dried mannitol and microcrystalline cellulose in the ratio 1:1 and 7% wt/wt Polyplasdone XL-10 showed faster disintegration, within 12.5 seconds, than the marketed tablet (112 seconds). Taste evaluation of RDT in human volunteers revealed considerable taste masking with the degree of bitterness below threshold value (0.5) ultimately reaching to 0 within 15 minutes, whereas ondansetron HCl was rated intensely bitter with a score of 3 for 10 minutes.
Bora et al (57) developed the taste-masked microspheres of intensely bitter drug ondansetron hydrochloride by spray-drying technique. The bitter taste threshold value of ondansetron hydrochloride was determined. Three different polymers viz. Chitosan, Methocel E15 LV, and Eudragit E100 were used for microsphere formation, and the effect of different polymers and drug-polymer ratios on the taste masking and release properties of microspheres was investigated. The taste masking was absent in methocel microspheres at all the drug-polymer ratios. The Eudragit microspheres depicted taste masking at 1:2 drug-polymer ratio whereas with Chitosan microspheres the taste masking was achieved at 1:1 drug-polymer ratio. The drug release was about 96.85% for eudragit microspheres and 40.07% for Chitosan microspheres in 15 min.

Ogawa et al (58) quantified the degree of suppression of the bitterness of two amino acids (L-isoleucine (L-Ile), and L-phenylalanine (L-Phe)) and examined the mechanism of this bitterness suppression. The test chemicals used were two sweeteners (sucrose, aspartame), NaCl, various acidic (L-aspartic acid, L-glutamic acid), or basic (L-histidine, L-lysine and L-arginine) amino acids, tannic acid and phosphatidic acid. The combination of L-arginine (L-Arg) and NaCl together was the most effective in reducing the bitterness of 100 mM L-Ile and L-Phe solutions in human gustatory sensation tests. Even in bitterness of 0.1 mM quinine solution, L-Arg was also successful in reducing the bitterness. This bitterness-suppression effect was specific to L-Arg and not to the other basic amino acids. No comparable taste-masking effect was observed for the acidic amino acids.
2.4 Literature review on Cetirizine hydrochloride

Elzainy et al (59) assessed the peripheral H₁-antihistaminic activity and extent of systemic absorption of cetirizine from liposomes applied to the skin. Cetirizine was incorporated into small unilamellar vesicles (SUV) and multilamellar vesicles (MLV) prepared using L-α-phosphatidylcholine hydrogenated (HPC), and into Glaxal Base (GB) as the control. In a randomized, crossover study, each formulation, containing 10 mg of cetirizine, was applied to the depilated backs of 6 rabbits (3.08 ± 0.05 kg). Histamine-induced wheal tests and blood sampling were performed before cetirizine application and at designated times for up to 24 h afterwards. Compared with baseline, histamine-induced wheal formation was suppressed by cetirizine in SUV only at 24 hours, in MLV from 0.5 to 24 hours, and in GB from 0.5 to 8 h (P ≤ .05). Wheal suppression by cetirizine in SUV at 24 h (91.7% ± 5.2%) and in MLV from 1 to 24 h (93.8% ± 2.2% to 76.2% ± 6.5%) was greater than in GB (36.5% ± 7.4% to 60.6% ± 14.2%) from 1 to 24 h (P ≤ .05). Faster onset, as well as greater and more persistent suppression was obtained from cetirizine in MLV.

Korsgren et al (60) compared topical and oral routes of administration of cetirizine regarding efficacy, plasma exudation, and systemic drug levels in a repeated allergen challenge model of allergic rhinitis. Oral cetirizine dihydrochloride, 10 mg once daily, and topical cetirizine dinitrate in a dose corresponding to 4.4 mg of the dihydrochloride salt twice daily were given to grass pollen-sensitive individuals for 12 days in a double-blind, placebo-controlled, crossover design. Nasal symptoms and peak inspiratory flow were recorded in the morning, 10 minutes after allergen challenge, and in the evening. The pharmacokinetics of the treatments was monitored in 8 patients. The remaining 28 patients were challenged topically with histamine 12 and 24 h after the final topical and oral cetirizine doses, respectively. Nasal lavage levels of alpha2-macroglobulin were determined to evaluate histamine-induced mucosal plasma exudation. Both treatments reduced symptoms 10 minutes after allergen challenge (P < .001 vs placebo). Neither treatment reduced morning and evening symptoms or nasal peak inspiratory flow. Topical, but not oral, cetirizine reduced histamine-induced plasma exudation (P < .01 vs placebo) when systemic drug levels were similar in the 2 treatment regimens. It was
concluded that topical and oral cetirizine reduced acute nasal symptoms produced by allergen challenges in patients with established chronic symptoms.

**Wood et al (61)** investigated the metabolism and pharmacokinetics of cetirizine, a new H1-receptor antagonist. Single oral doses of 14C-cetirizine dihydrochloride (10 mg) in aqueous solution were administered to six healthy male volunteers. The drug was rapidly absorbed: The peak mean concentration of radioactivity (359 ng-equivalents/ml) and of unchanged drug (341 ng/ml) were achieved within one hour. Mean concentrations of cetirizine declined biexponentially and had a mean elimination half-life of 7.4 hours. The drug was excreted quite rapidly, with 60% of the dose recovered in the 24-hour urine. An additional 10% was excreted in urine over the next four days. Approximately 10% of the dose was excreted in feces over the five-day study period. The dose was excreted mainly as the unchanged drug. Examination of the radioactive compounds present in the plasma, and excreted in the urine and feces indicated little metabolism of cetirizine. One minor metabolite, formed by oxidative O-dealkylation of the cetirizine side chain, was detected in plasma and feces.

**Awni et al (62)** studied the pharmacokinetics of Cetirizine, a histamine H1-receptor antagonist in five renal failure patients undergoing chronic haemodialysis therapy. The patients received one 10 mg cetirizine dihydrochloride capsule 3 h before haemodialysis. Concentrations of cetirizine in serum and dialysate were determined by HPLC. The maximum serum cetirizine concentration and the time to reach that maximum were 285 µg/l and 2.0 h, respectively. The terminal disposition half-life of cetirizine in these patients was 19.3 h. The haemodialysis clearance of cetirizine was 14.0 ml/min. Although this is approximately 33% of the apparent total body clearance of cetirizine in subjects with normal renal function, the fraction of the dose removed by dialysis was only 9.4%. Thus, since haemodialysis does not produce a clinically significantly alteration in cetirizine elimination, no supplemental dose should be necessary after dialysis.

**Drozd J et al (63)** described a method for the determination of cetirizine hydrochloride in pharmaceuticals by first, second, third and fourth order derivative spectroscopy using peak-peak and peak-zero measurements. The calibration curves are linear within the
concentration range of 7.5-22.5 µg/ml for cetirizine dihydrochloride. The procedure is simple, rapid and the results are reliable.

**Walily et al (64)** developed derivative spectrophotometric, colorimetric and HPLC methods for the determination of cetirizine dihydrochloride in tablet form. Cetirizine hydrochloride was determined by its first and second derivative amplitudes at 239 (peak) and 243-233 nm (peak to trough) respectively. Second derivative method was found to be most sensitive. The HPLC and spectrophotometric methods were found to be reproducible. All proposed methods were linear with good reproducibility and sensitivity.

**Jaber at al (65)** developed and validated HPLC method for determination of cetirizine hydrochloride, related impurities and preservatives in commercial oral solutions and tablet dosage forms. The two preservatives determined by this method were propyl and butyl parabens. The chromatographic system used was equipped with a Hypersil BDS C18, 5 micron column (4.6 x 250 mm) and a detector set at 230 nm in conjunction with a mobile phase of 0.05 M dihydrogen phosphate:acetonitrile:methanol:tetrahydrofuran (12:5:2:1, v/v/v/v) at a pH of 5.5 and a flow rate of 1 ml/min. The calibration curves were linear within the target concentration ranges studied, namely, 2 x 10(2) - 8 x 10(2) µg/ml and 1-4 µg/ml for cetirizine hydrochloride, 20-100 µg/ml for preservatives and 1-4 µg/ml for cetirizine hydrochloride related impurities. The method proved to be specific, stability indicating, accurate, precise, robust and could be used as an alternative to the European pharmacopoeial method set for cetirizine hydrochloride and its related impurities.

**Makhija et al (66)** developed and validated a rapid, selective high performance thin layer chromatographic method for simultaneous estimation of pseudoephedrine and cetirizine in pharmaceutical dosage forms. The method employed TLC aluminium plates precoated with silica gel 60F-254 as the stationary phase. The solvent system consisted of ethyl acetate-methanol-ammonia (7:1.5:1, v/v/v). This system was found to give compact spots for both pseudoephedrine (Rf value of 0.69+/−0.01) and cetirizine (Rf value of 0.38+/−0.01). Spectrodensitometric scanning-integration was performed at a wavelength of 240 nm. The polynomial regression data for the calibration plots showed good linear
relationship with \( r^2=0.9947 \) in the concentration range of 10-26 µg for psuedoephedrine and 200-1200 ng for cetirizine with \( r^2=0.9973 \).
2. Literature review

2.5 References:


2. Literature review

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2. Literature review


2. Literature review


