2.1 Literature Review on Effervescent Tablet Formulation

1. Ely et al developed a new type of respiratory drug delivery carrier particle that incorporates an active release mechanism. Spray drying was used to manufacture inhalable powders containing polybutylcyanoacrylate nanoparticles and ciprofloxacin as model substances for pulmonary delivery. The carrier particles incorporated effervescent technology, thereby adding an active release mechanism to their pulmonary route of administration. Effervescent activity of the carrier particles was observed when the carrier particles were exposed to humidity. Gas bubbles caused by the effervescent reaction were visualized by confocal laser scanning microscopy. The effervescent formulation the average mass median aerodynamic diameter was 2.17 μm ± 0.42, fine particle fraction was 46.47% ± 15%. The results also showed that the effervescent carrier particles released 56 ± 8% ciprofloxacin into solution compared with 32 ± 3% when lactose carrier particles were used. In conclusion, effervescent carrier particles can be synthesized with an adequate particle size for deep lung deposition. This opens the door for future research to explore this technology for delivery of a large range of substances to the lungs with possible improved release compared to conventional carrier particles (Ely et al. 346-53).

2. R. Wiwattanapatapee et al studied effervescent fast-disintegrating granules containing endospores of Bacillus megaterium were developed for use either by broadcast or spray application. The formulation composed of lactose, polyvinyl pyrrolidone K-30 (PVP, K-30) and effervescent base (citric acid, tartaric acid and sodium bicarbonate). The number of living bacteria in effervescent granules that performed mycelial growth inhibition was in the range of 109 CFU/g after 12 months storage at room temperature. The number of viable bacteria after applying into the water and spraying on the rice seedling for 7 days in the greenhouse tests were also satisfactory high. The scanning electron microscope (SEM) was used to observe bacterial antagonist on the surface of leaf sheath and leaf blade after spraying with formulation. Effervescent formulation applied either broadcasting or spraying reduced incidence of sheath blight disease in the greenhouse experiments (Wiwattanapatapee et al. 229-35).
3. Rotthäuser et al evaluated the physical properties of effervescent tablets. Effervescent tablets were prepared by direct compression which was lubricated using spray dried l-leucine and polyethylene glycol 6000. Residual force, crushing strength and disintegration time are considered as response variables and related to the l-leucine and polyethylene glycol concentrations and to the compression force. The calculated models are used to assess the influence of the production factors on tablet properties. As increasing amounts of l-leucine, showing good lubricating properties, reduce the crushing strength and prolong tablet disintegration, the l-leucine concentration is kept at a low level. An optimum tablet formulation contains 2% l-leucine and 3% polyethylene glycol 6000. The tablets have a tensile strength of 0.47 MPa and disintegrate in less than 2 min. Predicted and experimental results are in agreement within a 95% CI (Rotthäuser, Kraus and Schmidt 85-94).

4. Yanze et al applied melt granulation in a fluidized bed dryer to manufacture one-step effervescent granules composed of anhydrous citric acid and sodium bicarbonate to make tablets. This study permitted us to establish that such process parameters as concentrations of polyethylene glycol (PEG) 6000, residence times in the fluidized bed dryer, fineness of PEG 6000, fineness of initial mixture effervescent systems, and efficiency of two lubricants markedly affect some granule and tablet characteristics. It is a dry process that is simple, rapid, effective, economical, reproducible, and particularly adapted to produce effervescent granules that are easily compressed into effervescent tablets (Yanze, Duru and Jacob 1167-76).

5. J. Amela et al studied moisture effect on ascorbic acid effervescent tablets. Therefore the choice of suitable excipients is a very important step in the formulation study of this type of tablets. This work reviews the most common excipients used in effervescent preparations. They are characterized by microscopical observation and determination of particle size distribution, density, moisture, hygroscopicity, and electrostatics. Hygroscopicity is the most important property when choosing an excipient for an effervescent preparation. Therefore, two different methods for its determination have been used (Amela, Salazar and Cemeli 407-16).
6. N. O. Lindberg et al formulated anhydrous citric acid and sodium bicarbonate was granulated with ethanol in an extruder. The effect of process variables on intragranular porosity and liquid saturation was investigated: powder flow rate, ethanol concentration, screw speed, die plate and screw configuration. Granule porosity was drastically prejudiced by screw configuration and ethanol concentration. Besides, the porosity was a so correlated with response variables that affected the decomposition of sodium bicarbonate. A more intense screw configuration enhanced the formation of carbon dioxide due to a temperature rise and consequently increased porosity. On the other hand, a higher ethanol concentration reduced the porosity. There was a strong correlation between intragranular porosity and liquid saturation (Lindberg et al. 1791-98).

7. P. Lotter et al evaluated two troubles of an undesirable nature were experienced in the formulation of effervescent multi-vitamin and mineral tablets. When tablets containing ascorbic acid, calcium carbonate and vitamins, combined with ordinary effervescent excipients and sodium benzoate as lubricant, were dissolved, fine needles formed during effervescence. These needles float on top of the solution, making the product unattractive. During effervescence of a second tablet containing magnesium oxide and calcium carbonate, combined with ascorbic acid, flake-like sediment formed. Infrared spectrophotometry, differential scanning calorimetry and atomic absorption analysis showed that the needles were benzoic acid, while the flakes were citrates - mainly calcium citrate. These problems were overcome by substituting the benzoic acid with micronised polyethylene glycol 6000 and by not including citric acid during the granulation stage but to add coarse citric acid crystals to the dry granules - composed of the rest of the tablet ingredients (Lötter et al. 1989-98).

8. Shery Jacob et al formulated fast-dissolving effervescent tablets by the modification of nonreactive liquid-based wet granulation technique. The presence of moisture was creating a problem for stable formulation. They developed glibenclamide effervescent granules which than compressed to make tablet at low compression force. polyethylene glycol was coated on citric acid which provide barrier for moisture absorption. The
The hygroscopic nature of PEG could decrease the attraction for moisture of effervescent mixtures by providing a stabilizing effect. The mixture of sodium bicarbonate and mannitol protect the sodium bicarbonate to react with citric acid. PEG 1000 melts at low temperature (~37°C) and allows the fast reaction between the acid source and base. The tablet prepared using citric acid and sodium glycine carbonate fast reaction and stability than citric acid–sodium bicarbonate tablet (Jacob, Shirwaikar and Nair 321-28).

9. Röscheisen et al formulated dried and milled L-leucine was compared as lubricants for effervescent tablet formulations with regard to their lubrication properties, disintegration time, and crushing strength. The quotient of compression force and residual force was used to calculate the lubricant effectiveness. The spray dried L-leucine was superior when compared to the milled type and was optimized for use in a direct compressible tablet formulation by a Simplex optimization. The results of the Simplex optimization were compared using summarizing equations with a 2’ factorial design. The combination of factorial design and Simplex method is a simple optimization strategy to reach the optimum, and to quantify the effects of the variables with a minimum number of trials (Röscheisen and Schmidt 133-39).

10. D. Nagendrakumar et al fast dissolving tablet of fexofinadine HCl by effervescent method. Effervescent tablet were made using citric acid and sodium bicarbonate as effervescent ingredients. He also use three different super disintegrates crospovidone, croscarmellose sodium and sodium starch glycolate in formulation. Directly compressible mannitol used in tablets which enhance the mouth feel. In final optimization he found that that formulation containing 8% w/w crospovidone 18% anhydrous citric acid and 24% sodium bicarbonate emerged as best formulation (Nagendrakumar et al. 116-19).

11. Ashutosh Mohapatra et al metformin patient friendly soluble effervescant tablet. Tablet made using combination of two acid source and normal NaHCO₃ heat treated NaHCO₃. Control heating of sodium bicarbonate form a sheath skin of sodium carbonate on bicarbonate nucleus leading to surface passivation which prevents onset of effervescant reaction in presence of moisture leading to stability. Ratio of citric acid and tartaric acid
in molar ratio 1:2 was found to be most stable as higher amount of least hygroscopic tartaric acid protect hygroscopic citric acid from the moisture. Formulation contain heat treated NaHCO$_3$ gave good result over other (Mohapatra, Parikh and Gohel 177).

12. P.V.Swamy et al developed pheniramine maleate orodispersible tablet with patient compliance by effervescent methods. Researcher used the sodium bicarbonate and tartaric acid along with different super disintegrating agents like pregelatinized starch, sodium starch glycolate, croscarmellose sodium and crospovidone. Formulation containing 4% w/w crospovidone and mixture of sodium bicarbonate and tartaric acid each 12% w/w come out as overall best formulation. Sort term stability study indicates the stable formulation (Swamy et al. 151-54).

13. Setty C.M. et al tried to formulate potassium citrate effervescent tablets by direct compression, fusion and wet granulation techniques. The results of this study show that wet granulation is a suitable method to produce effervescent tablets of potassium citrate due to the large size of these tablets in the pharmaceutical industry. Wet granulation is one of the most common methods used for granulation in the industry. This method is obtained by adding a solution with (or without) adhesive to the powder to form a wet mass. In this study, the prepared tablets were acceptable under the terms of pharmacopoeia standards only when PVP was added as a binder during the granulation process (Setty et al. 180).

14. Patent 5,962,022 (1999) assigned to SmithKline Beecham (Brentford, GB) describes an invention that relates to pharmaceutical compositions for oral administration of antibiotics and other medicament with unpleasant taste characteristics and particularly to compositions formulated as tablet. This chewable composition was especially suitable for improving the taste characteristics of range of medicament, particularly for improving the taste of bitter tasting medicament and also provided a pleasant mode of administrating medicament, particularly those with unpleasant mouth feel even in the absence of a bitter taste e.g. antacids. The effervescent couple comprises a basic ingredient and an acidic ingredient. The basic ingredient liberates carbon dioxide when it comes in contact with acidic ingredient and saliva or added to water. The effervescent
couple typically comprises of citric acid or sodium hydrogen citrate and sodium bicarbonate. Another aspect of this invention is incorporation of disintegrants that gives the patient an option of dispersing the tablet in small amount of water prior to administration (Bolt, Merrifield and Carter).

15. Patent 6,245,353 (2001) describes an invention that provides a novel and therapeutically advantageous solid, rapidly disintegrating, effervescent, rapidly dissolving dosage form for oral administration of cetrizine. The dosage form contains organic edible acid, alkali metal and an alkaline earth metal carbonate and bicarbonate and optionally a pharmaceutically acceptable auxiliary ingredient along with the drug. The formulation of this invention when dissolved in water, yields a solution having a pleasant taste with improvement in patient compliance. This obviates the need of tedious process of coating the individual crystal of cetrizine for masking the bitter taste. The patent describes the first ever effervescent preparation of cetrizine, which is very effective against allergic disorders (Tritthart and Piskering).

16. Another patent 6,242,002 (2001) describes rapidly disintegrating oral dosage form. Patients suffering from Parkinsons disease usually have problem due to strong tremors when swallowing a tablet with a liquid. Also, administration of tablet for a patient having swallowing difficulty is not possible. The object of rapid disintegration of Selegiline (an antipakinsonian drug) was achieved by rapidly disintegrating oral dosage form (with or without water) as an effervescent formulation comprising an alkali sensitive drug and an effervescent base of an alkaline earth metal carbonate, an organic edible acid and an alkali metal salt of citric acid and optionally, a pharmaceutically acceptable auxiliary ingredient. This invention discloses an effervescent formulation that can be in the form of granules or tablets. The tablet can also be buccal tablet. By addition of water or contact of such effervescent formulation with saliva, results in a suspension or solution with carbon dioxide evolution and such suspension or solution has a pleasant taste. It also aids in rapid release of ingredients (Tritthart, Piskernig and Kolbl).
17. Patent 6,099,861 (2000) describes a water soluble effervescent tablet formulation for preparing a disinfecting solution. The formulation comprises of a first tablet containing bromide releasing agent and a second tablet containing a hypochlorite releasing agent. This invention discloses an effervescent tablet formulation that can be used to prepare a disinfectant solution wherein the formulation avoids the disadvantages and the problems such as difficulty in storage, mixing and handling of concentrated halogens and instability in diluted forms. The formulation described in the patent can be added directly to water to prepare a disinfectant solution (Desenna and Dawson).

18. Patent 6,077,536 (2000) describes amoxicillin that is not in salt form, can be provided as an effervescent formulation in which it is solubilised upon contact with water providing a clear solution for oral administration. The amoxicillin hydrate is preferred over the trihydrate form and may be present in conjunction with a beta lactamase inhibitor, such as clavulanic acid or its potassium salt. The formulations are typically in form of free flowing powders or granules or tablets (Desenna and Dawson).

19. Another patent 6,051,254 (2000) stated a granular formulated using amoxicillin hydrate, and an effervescent materials. The more amount of alkaline material solubilized the drug and effectively reacted with acid. The other material in formulation was also added like flavoring agent to enhance the palatability of formulation (Merrifield, Carter and Doughty).

20. Patent 6,132,770 (2000) describes a new multiple unit effervescent dosage form containing an acid susceptible proton pump inhibitor and also contains a separate second component, at least one effervescent tablet constituent. The core material is in the form of pellets covered with an enteric coating layer having mechanical properties such that the acid resistance of the enteric coated pellet is not significantly affected by compression of the pellets with the other tablet components during tabletting. The patent further describes the method for manufacture of such a formulation and use of such formulation in medicine (Lundberg).
21. Patent 6,171,617 (2001) discloses a clearly dissolving ibuprofen effervescent formulation and a process for the preparation of this formulation. The drugs for pain relief should be made available at reasonable prices. But the water soluble salts of ibuprofen such as ibuprofen-lysinate and ibuprofen-sodium lysinate are very expensive as compared to ibuprofen itself and other widely used analgesics such as aspirin and paracetamol. Ibuprofen is an organic acid having poor water solubility. The invention describes an effervescent formulation containing two separately produced granules: 1) ibuprofen granules prepared using ibuprofen and a basic adjuvant I molar ratio of 1:5-10 and 2) ibuprofen free effervescent granules containing an acid component and a carbon dioxide generating component (Gruber).

22. Patent 6,190,697 (2001) describes an effervescent formulation in form of granules and tablets containing effervescent base and at least one water soluble or suspendable plant extract whose particles are coated with oily, fatty or waxy substance. It also contains one emulsifier and antifoaming agent in the coating and/or as a component of mixture. As a result of coating treatment the plant extract becomes sufficiently hydrophobic to prevent the conversion of the effervescent tablet into a paste upon dissolution in water. When in contact with water, the effervescent particles generate carbon dioxide and the plant extract particles are ejected from the tablet owing to the hydrophobic structure and dissolve slowly. In order to obtain appropriate suspension, stabilizer was added (Gergely et al.).

23. Patent 5,948,439 reports effervescent granule preparation for the release and efficient dispersion of herbal medicines into bathing water for topical application or into steam for inhalation. These effervescent granules enable both herbal extracts and essential oils to be evenly and efficiently dispersed in water. This is particularly beneficial for the oils that do not disperse well in water (Forman et al.).

24. Patent 6,200,604 (2001) describes a dosage form adopted to supply medicament to the oral cavity for buccal, sublingual or gingival absorption of the medicament which contains an orally administrable medicament in combination with an effervescent couple for use in promoting absorption of the medicament in the oral cavity. The use of
an additional pH adjusting substance in combination with the effervescent couple is also described (S. I. Pather et al.).

25. Patent 6,284,272 (2001) discloses a technique that enables preparation of effervescent tablet and can have direct industrial application. It is based on the use of a particular effervescent blend of acids and sodium glycine carbonate, present in sufficient amount to rapidly disperse and assist dissolution of the formulation. According to another aspect of the invention, it was found that the use of blend of certain acid with sodium glycine carbonate allows preparing effervescent tablets by direct compression in normal thermo-hygrometric condition and with standard tableting equipment. This technology is also applicable to active ingredients or excipients that cannot be wet granulated or which contain a residual percentage of hardly eliminable water of crystallization (Chiesi et al.).

26. Another patent 6,066,335 (2000) describes a method of producing effervescent tablet which consists of at least one active ingredient, one binder and sherbets wherein propylene glycol or glycerin is used as binder. The sherbets are added to this mixture in an air conditioned atmosphere and the mixture is formed into tablets. This method produces mechanically stable effervescent tablets with a high dissolving velocity. An important advantage of this method is the requirement of small apparatus and short processing time. The method is applicable to prepare pharmaceutical tablets as well as effervescent tablets for washing and bathing (Machoczek).

27. Patent 6,294,579 (2001) describes a method of delivery of Tyrosine supplement to human body. The problem with tyrosine supplements is that accurate dosage is difficult to achieve. This is so because tyrosine does not dissolve well in water or other neutral pH liquids and is very acid labile. This results in erratic absorption and inconsistent results. This invention describes the method of promoting tyrosine availability to the body in effervescent form that allows tyrosine to dissolve and disperse in to solution upon activation with water. The increase in solubility and dispersal gives a more uniform absorption of the product after ingestion. The effervescent form of tyrosine buffers stomach acid thereby inhibiting destruction of tyrosine (Carnazzo).
28. Patents 6544557 (2003) an effervescent sub-lingual type composition, optionally in tablet form, comprising at least one active ingredient, one or more fruit acids, and one or more effervescing alkalis, wherein at least the acid component(s) have been coated with protective layer of polydimethylsiloxane that substantially minimizes contact between the acid(s) and atmospheric moisture until the composition is purposely mixed with water or is used sub-lingually. A method of preparation of the effervescent compositions is also disclosed (Selim).

29. Patent 6565881 (2003) the present discovery relates to a new type of solid preparations for cosmetic, hygienic and therapeutic use, which has both the properties of a solid bath additive and those of liquid products, and is characterized especially by the addition of lipid components, vesicle forming lipids, tensides and, in some cases, mineral salts. Active components, adjuvants such as stabilizers, adsorbing substances, lubricants as well as smoothing and breakdown promoting agents may also be contained therein (Nürnberg et al.).

30. Patent 6649186 (2003) explained here effervescent granules with a controllable rate of effervescence. In some embodiments, the granules comprise an acidic agent, an alkaline agent, a pharmacologically active agent, hot-melt extrudable binder capable of forming a eutectic mixture with the acidic agent and, optionally, a plasticizer. The effervescent granules are made by a hot-melt extrusion process. The present invention also provides a thermal heat process for preparing a pharmacologically active agent containing effervescent granule. In certain aspects, the granules contain pharmacologically active agents such as narcotics, antidiarrheal agents, antiviral agents, anxiolytic agents, a cholesterol lowering agent, an alpha adrenergic blocking agent, a phenanthrene derivative. By way of example, some of the narcotics that may be included in the granules and in the process of preparing the granules include, by way of example: phenanthrene derivatives (e.g., morphine sulfate), and morphine derivatives (e.g., hydromorphone hydrochloride) (Robinson, Mcginity and Delmas).

31. Patent 6974590 (2005) the dosage form adapted to provide a medicament to the oral cavity for buccal, sublingual or gingival absorption of the medicament which contains
an orally administrable medicament in combination with an effervescent for use in promoting absorption of the medicament in the oral cavity. The use of an additional pH adjusting substance in combination with the effervescent for promoting the absorption drugs is also disclosed (S. I. Pather et al.).

32. Patent 7390503 (2008) an ondansetron solid orally disintegrating dosage form for oral administration with water-dispersible component or water-insoluble cellulose derivative and a disintegrating agent and lubricant. The lubricant was a possible a combination of magnesium stearate, sodium stearyl fumarate and colloidal silicon dioxide (Ahmed, Gorukanti and Chowdhury).

2.2 Literature Review on Effervescent Pellets Formulation

1. Patent 6,432,450 (2002) describes the effervescent tablets or granules packed in sachets are often difficult to handle. When in contact with water, the components of the effervescent system start to react producing effervescence. This effect is amplified when the granules are poured from a commercial sachet, which in most of the cases close to square shape and for this reason has a relatively wide tear opening. The components of the effervescent mix then hit a correspondingly large part of the liquid surface forming a relatively thin layer. This patent states that the effervescent granules with delayed effervescence consist of at least one acid component and one component evolving gas under the action of acid as well as of active substance, fragrances, plant extracts, vitamins, minerals etc. admixed as needed. The gas evolving components include alkali hydrogen carbonate, alkali carbonate and/or alkali earth carbonates particles which are coated with melt of polyethylene glycol 6000. The particle size is above 0.2 mm (Gergely, Gergely and Gergely).

2. Patent 6,071,539 (2000) describes the effervescent granules having a controllable rate of effervescence prepared by hot melt extrusion of acidic agent , alkaline agent and a hot melt extrudable binder having melting or softening point below 150° C and capacity to form eutectic mixture with the acidic agent. A formulation according to this invention can provide a rate of release of an active ingredient that ranges from immediate to a delayed or controlled release over a prolonged period of many hours.
According to one of the aspect of this invention, it has been found that combination of the effervescent granules with the other ingredient can provide effective taste masking of particularly poor tasting compounds. This aspect of the invention provides a dosage form which offers both immediate or extended release and effective taste masking (Robinson and Mcginity).

3. Patent 6,488,961 (2002) disclosed effervescent granules having a controllable rate of effervescence i.e. a rapid, intermediate or slow. The rate of effervescence of the effervescent granule can be controlled by 1) varying the relative amounts of the components, 2) optionally forming a eutectic mixture between the acidic agent and hot-melt extrudable binder, 3) varying acidic to alkaline agents ratio, 4) hydrophilicity vs hydrophobicity of the binder, 5) varying the effervescent couple to hot melt extrudable binder ratio and 6) varying the amount of plasticizer present. Hot melt extrudable binder which can be used in effervescent granules include acacia, tragacanth, gelatin, starch, cellulose, polyethylene glycol, guar gum etc (Robinson and Mcginity).

4. Patents 6,350,470 (2002) describes the use of effervescence as a penetration enhancer for drugs known or suspected of having poor bioavailability. Effervescence can occur in the stomach, once the tablet or any other dosage form is ingested. In addition to effervescence in the stomach, the effervescence can occur in any other part of gastrointestinal tract such as esophagus, duodenum and colon, by use of appropriate coatings. The site of effervescence and drug release is chosen to correspond with the segment of the gastrointestinal tract displaying maximal absorption of the formulated drug, or to gain some other therapeutic advantage (I. S. Pather et al.).

5. Sinha et al studied the effect of different grades of microcrystalline cellulose. He also evaluated the effect of filler with different proportions of fillers like lactose and dicalcium phosphate dihydrate (DCPD) were also compared the effect of these fillers on the pellet properties. By keeping the amount of water constant for granulation of Avicel/ Avicel and evaluate and quantitative the influence of these excipients/fillers on the pellet properties. The various pellet properties evaluated included, drug release, size and size distribution, shape, density, friability and flow. Average diameter of did not
change within the Avicel grades and Avicel PH 101 and lactose was more or less similar in mean diameter. The same happening was observed in case of DCPD as well. Pellets prepared using lactose was larger so it concluded that the presence of Avicel suppressed the change in pellet size. By SEM photograph suggested the Avicel PH 101 gave round shape of pellets with compare to Avicel PH 302 were dumbbell shaped. Drug release rate varied in all the formulations. But in the Avicel grades, Avicel PH 302 showed the long time drug release where as Avicel PH 101 showed the least. By increase the amount of filler it increase the drug release. Less water was required for preparation containing higher amounts of lactose and DCPD. DCPD alone failed to spheronize, although pellets of plain lactose could be formed at the investigated level of water (Sinha, Agrawal and Kumria 1-8).

6. Chamsai and Sriamornsak formulated novel disintegrated MCC pellets with improved drug release of low water soluble drug indomethacin. As granulating liquids containing of PEG 400, polysorbate 80, ethanol and water were added for pellet preparation. In the formulation, Tween 80 as surfactant, PEG 400 as solubility enhancement, CCS as super disintegrating agent was incorporated. MCC alone not increase the disintegration. Whereas use of CCS, tween 80, PEG 400 gave fast disintegration. Their drug dissolution was also improved greatly. At last he concluded that the disintegrating/exploding MCC pellets are promising for enhancing drug dissolution of indomethacin or other poorly water-soluble drugs (Chamsai and Sriamornsak 278-85).

7. Nadia Passerini et al prepared pellets by melt granulation, ibuprofen as a poorly water soluble model drug in order to improve its dissolution rate and its availability; lactose as a diluent and poloxamer 188 (Lutrol F68), as a new meltable hydrophilic binder, were used. The granules were prepared in a laboratory-scale high-shear mixer, using a jacket temperature of 50°C and an impeller speed of 500 rpm. The particle size analysis shows that the main fraction was between 200 and 500 mm, while the determination of drug content pointed out that ibuprofen was quite uniformly distributed in all the fractions. Scanning Electron Microscopy (SEM), image and fractal analysis discovered that the granules did not have a perfect spherical shape and a rugged surface (D 52.6475). The in vitro dissolution test showed an increase in the dissolution rate of
granules compared to pure drug and physical mixture. Stability studies indicated that the granule properties do not change, at least after 1 year of storage at 25°C. The results of this work suggest that the melt granulation technique is an easy and fast method to improve the dissolution rate of ibuprofen, using poloxamer 188 as a new hydrophilic meltable binder (Passerini et al. 71-78).

8. Abdalla and Mäder prepared the self emulsifying pellets and Diazepam as model drug. Solutol as meltable binder with MCC as pelletizing material. A self emulsifying pellet was prepared by Melting of GMS and Solutol at 70°C. Dissolving the model drug and the dye in the molten blend. Addition of water to the molten lipid blend until a creamy mass is produced. Cooling to room temperature. Addition of the dry MCC and mixing in a kneader for 15 min. Further addition of water until a mass suitable for extrusion is obtained. The pellets are capable of transferring lipophilic compounds into the aqueous phase and have a high potential to increase the bioavailability of lipophilic drugs. Spherical pellets with low friability and self-emulsifying properties can be produced by the standard extrusion/spheronization technique (Abdalla and Mäder 220-26).

9. H. Kranz et al prepared pellet using MCC and carrageenan as pelletizing agent in the formulation. Theophylline and vatalanib succinate used as model drug and croscarmellose sodium as super disintegrating agent. Hydroxyl propyl methylcellulose was used to coat the pellets. MCC pellets decrease the drug release and drug solubility. Addition of disintegrant increase drug mobility only small amounts of pore former Carrageenan-based pellets are much more porous and quickly disintegrate upon contact with aqueous media, resulting in fast release, even in the case of high dosed drugs with low/poor aqueous solubility (Kranz et al. 302-09).

10. Helton Santos et al formulated xanthan gum pellets and convert those pellets in tablet to study compaction, compression and drug release. Lactose monohydrate, tribasic calcium phosphate and β-cyclodextrin as filler. Pellets were prepared by extrusion–spheronisation. Ethanol/water mixture 50% (v/v) was used as the binding liquid. Tablets made of xanthan gum pellets comprising lactose or β -cyclodextrin did not
function as multiparticulate systems. Drug release was controlled using xanthan gum. tribasic calcium phosphate give good matrix integrity in tablet (Santos et al. 271-81).

11. Chatchawalsaisin et al formulated pellets using MCC and glyceryl monostearate with four different drug (Diclofenac sodium, Paracetamol, indomethacin, ibuprofen). Water used as binder liquid for it. Glyceryl monostearate do not increase dissolution of drug. But it can reduce the amount of water required for binding. The porosity of the pellets of the different formulations generally decreased with the increase in water used to prepare the pellets, the extent of this decrease being dependent on the drug and the level of glyceryl monostearate. The in vitro drug release from the pellets was controlled by the solubility of the drug, the lower the value of the solubility, the longer the mean dissolution time (Chatchawalsaisin, Podczeck and Newton 35-48).

12. Quintavalle et al prepared sustained release co-extrudates by hot-melt extrusion and mathematical modeling of in vitro/in vivo drug release. Pellets were prepared using microcrysalline wax, PEG 6000, lactose and Theophylline drug candidate. microcrysalline wax and PEG 6000 use as meltable binder. Co-extrusion consists of the simultaneous extrusion of two or more materials creating a multi-layered extrudate, the shape of which depends on the design of the die. mathematical model proved to be reliable for what concerns both in vivo and in vitro experimental data description (Quintavalle et al. 282-93).

13. Ingunn Tho et al studied new use of Pectinic acid as pelletizing aid for preparation of pellets by extrusion shperonization. Developed formulations containing pectinic acid and lactose in the different ratio. Pectinic acid had good capability to make pellets in spherical shape even in low concentration. All formulated pellets had good hardness, aspect ratio and drug release with low water soluble drug in within 15 min both in simulated gastric acid and intestinal fluid. It showed that pectinic acid had a great capacity as an extrusion aiding excipient for pelletisation by extrusion/spheronization (Tho, Sande and Kleinebudde 95-99).
14. Alvarez et al studied compared powdered cellulose and microcrystalline cellulose as only excipients in the preparation of furosemide pellets by extrusion–spheronization. Pellets prepared with powdered cellulose and 25 or 50% furosemide showed smaller mean size, a wide-ranging particle size distribution, similar sphericity, greater surface unevenness and higher friability than equivalent pellets prepared with MCC. Furosemide release rate was markedly higher from powdered cellulose pellets, which may be attributable to their higher microspore volume. Scientists also noted that the mechanical properties, size and size distribution of pellets prepared with powdered cellulose are less apposite than those of pellets prepared with microcrystalline cellulose (Alvarez et al. 291-95).

15. H. Steckel, developed chitosan pellets were using extrusion/spheronization technology. They also used microcrystalline cellulose as additive in concentrations from 70 to 0%. Wet mass was prepared using water and diluted acetic acid in different powder to liquid ratios. The effects on pellets formation using water and different acetic acid concentrations and solution quantities were analysed. Also, the morphological and mechanical properties of the obtained pellets were investigated. With demineralized water as granulation fluid, pellets with a maximum of 50% (m/m) of chitosan could be produced. The mass fraction of chitosan within the pellets could be increased to 100% by using diluted acetic acid for the granulation step. Increasing concentration of chitosan leads to increased porosity of pellets. In preparation of pellets, amount of acetic acid concentration increased which cause the steamy and rod shape pellets (Steckel and Mindermann-Nogly 107-14).

16. Aleksandra Dukic Ott et al studied modified starch for pelleting aid with poorly soluble drug and HPMC as binder in different concentration. Scientists optimized formulation by $2^4$ factorial designs. Bioavailability study was performed on dog. They concluded that the oral bioavailability was similar that of the immediate fast dissolving tablet (Dukić-Ott et al. 715-24).

17. C. Vervaet et al explored the use of other materials as pelleting aid for extruder spheronizer. MCC is a prime material for the pelleting aid. This gave good quality of
pellets. But it has some limitation or compatibility issue, which lead to find the alternate source of MCC. He gather other pelletizing source like powdered cellulose, starch, chitosan, kappa-carrageenan, pectinic acid, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, polyethylene oxide, cross-linked polyvinylpyrrolidone, glycerol monostearate. Even though long list of other material as alternate to MCC but they did not gave flexibility in formulation and processing (Dukić-Ott et al. 38-46).

2.3 Literature Review on Evaluation of Effervescent Formulation

1. Lampl et al studied individual data pooled analysis provided evidence that 1,000 mg eASA is as effective as 50 mg sumatriptan for the treatment of acute migraine attacks and has a better side effect profile. This is also true for patients with moderate as well as severe migraine headache pain at baseline. Therefore, patients should be advised to treat migraine attacks first with eASA and use a triptan in case of no response (Lampl, Voelker and Diener 705-12).

2. L. M. Ross-Lee et al formulated Single doses of effervescent tablets and enteric coated tablets of acetylsalicylic acid (ASA) were given to healthy volunteers in random order. Plasma ASA and salicylic acid (SA) levels were measured and concurrent in vitro measurements of the volunteers' platelet aggregation were carried out. The effervescent preparation resulted in peak ASA concentrations of 17-40 mg/l, achieved 20 to 30 min after a 1200 mg dose, whereas peak ASA levels of 0.01-0.37 rag/l were observed 4-6 h after a 650 mg dose of the EC preparation. With all the aggregating agents that were added to the test system maximum inhibition of platelet aggregation (about 50% of pre dose levels) was seen 1.0 h after the effervescent ASA dose, and persisted to at least 24 h, but with the EC preparation not until 24 h, at which time the degree of inhibition was also about 50% of pre-dose levels. A 1.0 g dose of sodium salicylate had no effect on in vitro platelet function. It was concluded that mean plasma levels of ASA of less than 0.25 mg/l are sufficient to depress aggregation by approximately 50%. A low dose of ASA taken daily either as effervescent ASA or EC ASA, significantly inhibits platelet aggregation and so may reduce the risk of ischaemic episodes in susceptible patients (Ross-Lee et al. 545-51).
3. T. Hummel et al compared the dose-related effects of both ibuprofen tablets and ibuprofen effervescent on phasic pain. Twenty volunteers participated in this randomized, double-dummy, vefold crossover study. Estimation were obtained before and 15, 60 and 240 min after drug administration. Pain was produced by CO$_2$ pulses applied to the left nostril. Subjects rated the intensity of the painful stimuli by means of a visual analogue scale. Ibuprofen decrease in pain-related potential amplitudes, indicating its antinociceptive effects. Blood concentration of drug was faster in effervescent ibuprofen tablet that conventional tablet that is 15±40 min and 60±90 min tmax after administration respectively (Hummel et al. 107-14).

4. K. Zahlsen et al compared the rate of absorption between conventional paracetamol tablets and effervescent paracetamol tablets. Methods: Twenty healthy volunteers participated in an open randomised crossover study and were given a 1000- mg dose of either ordinary paracetamol tablets or effervescent paracetamol tablets with a 3-week washout period in between. Blood samples were collected for 3 h. The mean tmax was 27 min in paracetamol effervescent tablets where as paracetamol tablets had 45 min. The mean AUC was significantly higher with paracetamol effervescent tablets than with ordinary tablets. After 15 min, 17 (85%) subjects in the effervescent group had a serum concentration of 70 µmol/l (lower therapeutic serum concentration) or higher relative to only 2 (10%) subjects in the ordinary tablet group (P . 0.001). Paracetamol effervescent tablets are absorbed significantly faster than ordinary paracetamol (Rygnestad, Zahlsen and Samdal 141-43).

5. Merckle and Kovar studied Near-infrared spectroscopy was used to determine acetylsalicylic acid (ASA) in three different effervescent tablet formulations. The nominal ASA concentrations were 14.9% in the single substance formulation, 17.4% in the combination with ascorbic acid and 8.7% in the combination with paracetamol and ascorbic acid. All three formulations were measured as intact tablets in diffuse transmittance and reflectance and as powdered tablets in diffuse reflectance. The relative standard errors of calibration achieved for the three NIR methods were between 1.20 and 2.01% for ASA Mono, between 1.91 and 2.21% for ASA C and between 2.41 and 4.50% for ASA Combi. The results obtained in transmittance mode were comparable with those obtained in reflectance mode, which is normally used in
NIRS. In the test sets of ASA Mono and ASA_C relative root mean square values between 2.21 and 3.13% were obtained. The three NIR methods applied are thus suitable for the quantitative determination of ASA in effervescent tablets and have the advantage over HPLC of being rapid and simply carried out with little sample preparation; they are nondestructive and do not require any environmentally harmful reagents (Merckle and Kovar 365-74).

6. Erdal Dinc analyzed the simultaneous spectrophotometric determination of ascorbic acid (AA) and acetylsalicylic acid (ASA) in effervescent tablets in the presence of the overlapping spectra was accomplished by the continuous wavelet transform (CWT), derivative spectrophotometry (DS) and partial least squares (PLS) approaches without using any chemical pre-treatment. CWT and DS calibration equations for AA and ASA were obtained by measuring the CWT and DS amplitudes corresponding to zero-crossing points of spectra obtained by plotting continuous wavelet coefficients and first-derivative absorbance values versus the wavelengths, respectively. The PLS calibration was constructed by using the concentration set and its full absorbance data consisting of 850 points from 220 to 305 nm in the range of 210–310 nm. These three methods were tested by analyzing the synthetic mixtures of the above drugs and they were applied to the real samples containing two commercial pharmaceutical preparations of subjected drugs. A comparative study was carried out by using the experimental results obtained from three analytical methodologies and precise and accurate results were obtained (Dinç, Ozdemir and Baleanu 569-75).

7. Sung et al studied a suitable capillary electrophoresis (CE) method was developed and validated for sulfate anion determination in effervescent tablets of Digedryl. The large excess of other ions in the matrix (i.e. excipients) constituted the main difficulty of this method’s development. So an original analytical procedure for both the conditioning and rinsing of the capillary was purposed including a running electrolyte constituted by boric acid 20 mM and hexamethonium dibromide 0.75 mM at pH 8.00. Separation was carried out on a 60.2 cm(50 cm to the detector) · 0.75 lm i.d. fused-silica capillary at a potential of -29 kV and 35°C. Indirect UV detection was performed at a wavelength of 254 nm using a background electrolyte containing potassium chromate. Nitrate anion
was used as an internal standard for quantification. This CE method was validated in terms of selectivity, linearity, accuracy and precision (Sung et al. 33-37).

8. Mona Darwish et al studied to assess the dose proportionality of effervescent tablet in healthy volunteers over the potential therapeutic dose range (100-800 pg) and characterize the pharmacokinetic (PK) profile of 4 doses (100, 200, 400, and 800 pg) of FEBT. Plasma fentanyl concentrations were measured from venous samples obtained over 72 hours after FEBT administration. Early fentanyl exposure was assessed using AUC from time 0 to 0.75 hour. Adverse events (AEs) were monitored and recorded throughout the study by medically qualified personnel. In this study of the dose proportionality of FEBT in healthy volunteers, the PK profile of FEBT was characterized by a high early systemic exposure of fentanyl (0.09-0.52 ng. b/mL). Dosedependent parameters increased in an approximately dose-proportional manner from 100 to 800 pg FEBT (Darwish et al. 707-14).

9. Mona Darwish et al studied to compare the relative bioavailability of FEBT 1080 lag with that of oral transmucosal fentanyl citrate (OTFC®) 1600 lag, and the secondary objective was to assess the dose proportionality of FEBT 270 to 1300 lag in healthy adult volunteers. In this pharmacokinetic study in healthy volunteers, total systemic exposure increased in a dose-proportional manner up to FEBT 1300 lag, whereas doses above 810 lag showed a less-than-doseproportional increase in Cn~x. The results suggest that fentanyl enters the systemic circulation to a significantly greater extent (C~ and AUC0~max, ) and significantly more rapidly (T) with FEBT compared with OTFC., Relative Bioavailability of the Fentanyl Effervescent Buccal Tablet (FEBT) 1080 pg Versus Oral Transmucosal Fentanyl Citrate 1600 pg and Dose Proportionality of FEBT 270 to 1300 pg (Darwish et al. 715-24).

10. Azarmi et al studied safety of a new inhalable effervescent carrier preparation containing model nanoparticles. The particle size of the nanoparticles before incorporation into the effervescent carrier and after dissolving the carrier powder was measured. The effervescent activity of the inhalable nanoparticle powder was observed when the powder was exposed to humidity. The particle size of the nanoparticles did
not change significantly after spray-freeze drying. The mass median aerodynamic diameter (MMAD) of the prepared powder was \(4.80 \pm 2.12\) mm, which is suitable for lung delivery. The animals that were treated with effervescent powder tolerated the administration without any changes in their morbidity scores. Our pilot study demonstrates that pulmonary nanoparticle delivery via effervescent carrier particles appears safe in the present animal model (Azarmi et al. 943-47).

11. J. Amela et al evaluated different methods for determining the carbon dioxide evolved from effervescent systems are described. In addition, a comparison between some of them is carried out when a stoechiometric mixture of L-tartaric acid and sodium bicarbonate reacts. The methods compared are: gravimetric, volumetric and gasometric. The gravimetric methods can be direct or indirect. The direct ones are based on taking in the carbon dioxide by a sorbent substance. The increase of weight after the absorption represents the CO, evolved. In the indirect gravimetric methods the amount of carbon dioxide is determined by substraction of the weight of the sample after and before the effervescent reaction. The volumetric methods are based on an acid-base titration. In the method used, the carbon dioxide released reacts with barium hydroxide. The excess of barium hydroxide is titrated with oxalic acid. It is possible to calculate then the carbon dioxide produced in the reaction from the volume of oxalic acid used. In the gasometric methods the volume of gas is directly determined by the displacement of a solution when the gas is released. The gasometric method seems to be the most efficient among the studied ones (Amela, Salazar and Cemeli 1019-36).

12. V.Saano et al studied the pharmacokinetics of two 200 mg ibuprofen (IP) film-coated tablets and 200 mg effervescent tablets were studied in cross-over fashion on 14 healthy volunteers. After ingestion of the novel film-coated tablet, absorption half life (0.6 h) was 42-50 X (p<0.05) shorter, \(C_{\text{max}}\), (24.6 mg/l) was 38-42 X (p<0.05) higher and \(t_{\text{max}}\) (1.4 h) was 33-36 X (p<0.05) shorter than after the older type film-coated tablet and after effervescent tablet, respectively. The bioavailability of IP was close to similar from the three preparations. IP was tolerated without side-effects. The faster absorption of IP from the new film-coated tablet may have therapeutic significance when rapid
onset of effect is desirable, e.g. in the treatment of fever and migraine (Saano et al. 491-97).

13. J. M. Engzelius et al studied was carried out to check the efficacy of ranitidine effervescent tablets and famotidine wafers. Efficacy was mainly determined by the time to adequate symptom relief for the first symptom episode. There was a statistically significant difference in favour of 150-mg ranitidine effervescent tablets in terms of time to adequate symptom relief and the proportion of patients who achieved adequate symptom relief for the first episode (Engzelius et al. 513-18).

14. S. T. David et al evaluated the effect of environmental moisture on the physical stability of effervescent tablets in foil laminate packages containing microscopic imperfections (openings) was examined. Packaged tablets were stored at different relative humidity (RH) and temperature conditions and evaluated for physical stability at predetermined time interval. Physical stability was assessed by noting if the tablet components reacted prematurely to yield soft tablet during storage. A penetrating dye solution test was used to determine if the foil packages contained imperfections which might allow transmission of moisture. The result of the investigation indicated that absolute moisture integrity of the foil package is required for product stability (David and Gallian 2541-50).

2.4 Literature Review on Chlorpheniramine Maleate

1. Yalcin Ozkan et al made the hydrogel of chlorpheniramine maleate using different cellulose to found the good percutaneous absorption and characterized by in vitro and ex vivo study. Hydrogel was formulated using various concentrations of polymers, including hydroxypropylmethylcellulose (HPMC), sodium carboxymethylcellulose (NaCMC) and methyl cellulose (MC). The in vitro permeation study was carried out using cellulose dialysis membrane. Whereas ex vivo study was carried out using ratThe passive permeation of CPM was affected by the polymer concentrations. The effect of each polymer on the release rate of CPM was skin as membrane. The formulation which was found maximum drug release through cellulose membrane further check by other different membranes like polyurethane membrane, rat skin and human skin. From
the different diffusion barriers rat skin was found to be best alternative to human skin. They concluded that the Chlorpheniramine maleate appear a suitable drug entity for developing diadermatic dosage forms (Tas et al. 605-11).

2. Kumar et al formulated floating matrix using different polymer. The matrix was formulated using Glycerol monooleate as gastro retentive carrier and Chlorpheniramine maleate and diazepam as model drug. They also studied the effect of floatability using different polymer like Poly ethylene glycol 4000, 10000 and stearic acid. They found that the water uptake was increasing if polar drug Chlorpheniramine maleate use in compare to non polar drug diazepam. Poly ethylene glycol increase the drug release up to some extent and stearic acid decrease the drug release. Finally they concluded that the suitability of excipients depending on the polarity of drug which help to modified floatability and release profile by Glycerol monooleate matrix (Kumar et al. 151-60).

3. Nora H. Al-Shaalan developed method for simultaneous estimation of phenylephrine hydrochloride and chlorpheniramine maleate. He studied first derivative UV spectrophotometer with zero crossing measurement; second method was first derivative of ratio spectra, third method was multivariate spectrophotometric calibration for the simultaneous determination of the analyzed binary mixture where the resolution is accomplished by using partial least squares (PLS) regression analysis and fourth was HPLC method. HPLC method was superior over spectrophotometric method in analysis of binary mixture of drugs. High quality resolution between the studied drugs and the chosen internal standard was obtained in a short analysis time using simple extraction procedure without interference of endogenous substances present in serum samples (Al-Shaalan 15-21).

4. Şenyuva and Özden determined multidrug form pharmaceutical dosage form by HPLC method. The formulation was containing paracetamol, phenylephrine HCl, and chlorpheniramine maleate. The method involves the use of a µBondapak CN RP analytical column at 22°C as the stationary phase with the mixture of acetonitrile and phosphate buffer (pH 6.22, 78:22) as the mobile phase. This study has revealed that UV detection is a sensitive, reliable, reproducible, and accurate method for the
determination of the active ingredients in pediatric cough–cold syrups, capsules, and tablets (Şenyuva and Özden 97-100).

5. Mazumder B. et al made microspheres of the chlorpheniramine maleate by oil-in-oil emulsion solvent evaporation method using the combination of ethyl-cellulose and cellulose acetate polymers in the ratio of 1:1. It was found that the prepared microspheres were spherical, free flowing, high percentage entrapment efficiency and high percentage yielding capacity. It can be concluded from this study that CPM could be made into controlled-release drug delivery system using ethyl cellulose and cellulose acetate (1:1 ratio) as retardant materials in the ratio drug to polymer of 1:3, surfactant concentration of 3\%, stirring speed of 1800 rpm and volume of continuous phase of 100 ml as optimum process parameter. The in-vitro controlled release of CPM from the prepared microspheres formulations have been established in this study. However, the in-vitro release characteristics of drug from the microspheres are subject to confirmation in animal and human studies for coming into conclusion of enhanced bioavailability and reduced dose frequency to improve patient compliance (Mazumder et al. 905-13).

6. Iman IS et al formulated the transdermal patch of the chlorpheniramine maleate. He made the patch using different bioadhesive polymers such as ethyl cellulose, cellulose acetate, and polyvinyl pyrrolidone with different plasticizers such as propylene glycol (PG) and polyethylene glycol 400 (PEG400). Patch was prepared though solvent evaporation method, evaluated for their physical and mechanical properties and then subjected to stability study to select the best formula to be evaluated \textit{in vitro} and \textit{in vivo}. The selected formulae were examined for CPM release in phosphate buffer saline pH 5.5 and also tested for CPM permeation through ear rabbit skin. The \textit{in vivo} study carried out on optimized formulation and commercial CPM oral tablets. The results showed that CPM transdermal patch has higher bioavailability than an oral tablet of the same dose, with lower plasma fluctuation and less administration frequency (Iman, Nadia and Ebtsam 17).
7. Bhoi G. S. et al developed the medicated chewing gum of chlorphrneramine maletate. Chewing gum is the convenient and effective means of rapidly administering chlorpheniramine maleate, as it is readily soluble, permeable and used to relieve symptoms of allergy, hay fever and common cold. Medicated chewing gum had been formulated using gum base, sorbitol, mannitol, magnesium stearate, lecithin, menthol. This medicated chewing gum was prepared by direct compression method and formulated by using various compositions of gum base and lecithin like 30-35-40 % and 5-10-15 % accordingly. The developed formulation was evaluated for both pre and post compression parameter of tablets. In the formulation Soya lecithin was used as a plasticizer and it was found that it acted on the drug release to some extent. When concentration of Soya lecithin was increased, drug release was also found to be increased (Bhoi et al. 1309-19).

8. Yewale CP et al developed fast dissolving tablet of chlorpheniramine maleate using cation exchange resins. The cation exchange resins were used for taste masking. Complexes of ion-exchange resin and Chlorpheniramine maleate were prepared by taking drug: resin ratios 1:1, 1:2, 1:3 and 1:4 (w/w). The optimum drug:resin ratio and the time required for maximum complexation was determined. Developed formulation was evaluated for the drug content, taste, drug release, FTIR, DSC and X-ray diffraction. In the results, he found taste was masked by ion exchange resins. Fast disintegrating tablets were developed depending upon percent complexation, release study at salivary and gastric pH, taste evaluation. Chlorpheniramine maleate: Indion-234 complex of ratio 1:2 was used release drug 94.77% in 30 min. The Effective taste masking can be obtained from drug resins complex in developed formulation for better patient compliance (Yewale et al. 367-76).

9. Kanth N. P. et al formulated the oral dissolving film of CPM. The film was prepared using different film forming polymer like different grade of hydroxyl propyl methyl cellulose (HPMC). Prepared film was evaluated for thickness, tensile strength, elongation, folding endurance, disintegration time, drug release etc. formulation containing HPMC E3 gave better drug release than other grade of HPMC. At the end it
was concluded that the develop formulation can be a potential novel drug dosage form for pediatric, geriatric and also for general population (Kanth, Prasad and Kumar 1859).

10. Bhatti A. et al made the tablets rapidly disintegrating in saliva of CPM. The taste masked granules were made by Eudragit E-100 by the extrusion method. Drug release at acidic pH was high as compared to pH 6.8. Prepared granules were compressed to made the tablets and SSG was used as a super-disintegrant. Panel testing data collected from 20 healthy volunteers indicate successful formulation of oral fast disintegrating tablets which had good taste and disintegrated in the oral cavity within 30s (Bhatti and Singh 80).

11. Matsyagiri L. et al developed mucoadhesive buccal tablets of Chlorpheniramine maleate. The tablets were prepared using carbopol-934p, HPMC K4M, sodium alginate and guar-gum by direct compression method. Buccal tablets were evaluated such as thickness, hardness, weight uniformity, content uniformity, swelling index, surface pH, ex vivo residence time, in vitro release. Tablets containing HPMCK4M with carbopol was found to exhibit least matrix erosion. Optimized formulation showed highest drug release and swelling index of 102.5% and 123.2%, respectively. The optimized formulation was compared with marketed conventional tablet (chloral), the conventional tablet release only 64.44 % for 6 hrs where as the optimized formulation released up to 102.5 %. Thus conclusion can be made that the stable mucoadhesive buccal tablets of chlorpheniramine maleate can be developed for the sustained release. Therefore, bioadhesive buccal delivery of chlorpheniramine maleate may be good way to bypass the first pass metabolism composed of (Drug: HPMCK4M) different ratios (Matsyagiri et al. 102-09).

12. Zaky A.A. et al Sublingual tablets using novel ternary phase superdisintegrants of CPM. The novel ternary phase developed by co-processed superdisintegrants via solvent evaporation method using crospovidone, croscarmellose and sodium starch glycolate in different ratios (1:1:1, 3:1:1, 1:3:1and 1:1:3) were prepared. The pre-compression parameters for flow properties of the prepared co-processed superdisintegrants were evaluated of physical mixture of superdisintegrants. The tablet
was prepared by direct compression methods. The tablets were evaluated for its disintegration time, wetting time, in-vitro dispersion time as well as hardness, weight variation, friability, drug content and in-vitro dissolution study. The formulations CP1 and PM1 containing 4% w/w co-processed and physical mixture of superdisintegrant respectively (1:1:1 mixture of crospovidone, croscarmellose and sodium starch glycolate) were considered to be best formulations, which showed the shortest disintegration time (6.29 and 6.31 sec), in-vitro dispersion time (18.67 and 18.83 sec) and wetting time (12.47 and 12.58 sec) respectively. As well as these promising formulae showed highest drug release (100 and 97.52 %) within two min. Finally, the promising formulae were compared with CPM sublingual tablet prepared using commercially available co-processed mixture of excipients containing superdisintegrant (PharmaburstTM500). By statistical evaluation it found significance differences in disintegration time, in-vitro dispersion time, wetting time and in vitro drug release (Elbakry et al. 125-34).

13. Mitra J. et al made the microspheres of CPM using alginate/chitosan particles prepared by ionic gelation (Ca2+ and Al3+) for the drug release. The effect of different chitosan and Ca2+ concentrations on taste masking and the characteristics of the microspheres were investigated. The microspheres were prepared using cross-linked insoluble complexes that precipitate, incorporating the drug. Formulations were characterized for particle size and shape, entrapment efficiency, FTIR, x-ray diffraction (XRD), and DSC, bitter taste threshold and in vitro drug release in simulated gastrointestinal fluids. The results of DSC, X-ray diffraction and FTIR showed the presence of several CPM chemical interactions with alginate and ions (Ca2+ and Al3+). The microsphere formulations showed desirable drug entrapment efficiencies (62.2-94.2%). Calcium/aluminum alginate retarded the release at low pH and released the drug from microspheres slowly at simulating intestine pH. The drug release duration and the release kinetics were dependent on the nature of the polymers, the cation concentrations, and valences. The drug release rate was decreased by an increase in chitosan and cation concentrations (Jelvehgari, Barghi and Barghi 39-48).
14. Valizadeha H. et al formulated chlorpheniramine maleate a microsphere formulation in order to mask the bitter taste. Microspheres was made with pH-dependent polymers (such as Eudragits S100, L100 and L100-55) and by the double emulsion solvent diffusion method. They made formulations with different drug/polymer ratio were prepared and were characterized by drug loading, loading efficiency, yield, particle size, XRD, FTIR and DSC. The in vitro release studies were performed in pH 1.2 and 7.4. The results showed that microparticles prepared with pH dependent polymers were slower release than the commercial tablet by statistical analysis. The results indicated that the microsphere formulation could be a promising drug carrier for masking the bitter taste of chlorpheniramine (Jelvehgari et al. 45-58).

15. Yuvraj Singh Negi et al synthesized pH sensitive interpenetrating polymeric network beads composed of chitosan, glycine, glutamic acid, cross linked with glutaraldehyde and their use for controlled drug release. The results shown amorphous dispersion of CPM in the polymeric matrix. The swelling behavior and drug release was carried out at pH 2.0 and pH 7.4. The swelling behavior and release of drug were observed to be dependent on pH, degree of cross linking and their composition. The results shown that the cross linked IPN beads of chitosan-glycine-glutamic acid might be useful as a vehicle for controlled release of drug (Rani, Agarwal and Negi 71-84).

16. Athanikar N. K. et al developed the method for the rapid quantitative analysis of chlorpheniramine in plasma, saliva and urine using HPLC. A diethyl ether or hexane extract of the alkalinized biological samples was extracted with dilute acid which was chromatographed on a reversed-phase column. Ultraviolet absorption at 254 nm was monitored for the detection and brompheniramine was employed as the internal standard for the quantitation. The effects of buffer, pH, and acetonitrile concentration in the mobile phase on the chromatographic separation were investigated. A mobile phase made of 20% acetonitrile in 0.0075 M phosphate buffer and injected at a flow-rate of 2 ml/min (Athanikar et al. 367-76).

17. Qi M. L. et al developed a simple, rapid and accurate, routine-HPLC method is described for simultaneous determination of Acetaminophen, Caffeine and
Chlorpheniramine maleate in a new tablet formulation Chromatographic separation of the three pharmaceuticals was achieved on a Hypersil CN column using a mobile phase comprising a mixture of acetonitrile, an ion-pair solution and tetrahydrofuran (13:14:87, v/v, pH4.5). The flow-rate was changed from 1.0 ml/min (in 0≈7.5 min) to 1.8 ml/min (after 3.5 min) was complete in <10 min (Qi et al. 295-98).

2.5 Literature Review of Promethazine
1. Patil SV formulated the fast disintegrating sublingual tablet of Promethazine HCl for the treatment of motion sickness i.e. nausea and vomiting during travel or when in motion. He formulated 9 batches using three superdisintegrants Crospovidone, L-HPC, and Kyron T-314 in three different concentrations. The tablets were prepared by direct compression technique and it was evaluated parameter listed in pharmacopeia. He concluded that the all formulations were found within the pharmacopieal limit. Optimized batch was disintegrating in 18 sec and 96.05% drug release in 10 min. after stability study, he found the stable formulation (Derle and Wagh 59-64).

2. Sharma S. et al made the promethazine theoclate fast-dissolving tablets for treatment of nausea and vomiting. Drug solubility was increasing by formulating solid dispersion with β-cyclodextrin, crospovidone, and camphor. Formulation was optimized by $3^3$ full factorial design and tablets were prepared by direct compression method. He evaluated the disintegration time, friability and drug release after 5 min as dependent factors. The optimized tablet should be prepared with an optimum amount of β-cyclodextrin (3.0 mg), camphor (3.29 mg) and crospovidone (2.61 mg) which disintegrated in 30 s, with a friability of 0.60 % and drug release of 89 % in 5 min. At the end it was concluded that using a methodical formulation approach, an optimum point can be reached in the shortest time with minimal efforts (Sharma, Sharma and Gupta 489-97).

3. Sandeep D. S et al developed the fast dissolving tablet of Promethazine HCl. Promethazine is an antiemetic drug especially used for motion sickness condition. Tablets was prepared by direct compression method and camphor was selected subliming agent in three concentrations of 2%, 5% and 10%. There is there different superdisintegrants sodium starch glycolate, crosscarmellose and tulsion 414 were used
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in ratios 5% and 10%. All prepared formulations were evaluated for different parameters like weight variation, hardness, friability, drug content, disintegration time, wetting time and \textit{in vitro} dissolution. He summarized that the all the formulations followed the pharmacopoieal limits. Finally he was concluded that the camphor is best subliming material with desired dissolution profile. The optimized formulation was contain 10%w/w of sodium starch glycolate with 10%w/w of camphor, gave 93% drug release within 10 minutes with 26 seconds disintegration time (Kavitha et al. 660-63).

4. Chacko et al design orodispersible tablet of promethazine theoclate using superdisintegrants crosspovidone and sodium starch glycolate and co-processed superdisinetgrants (CP:SSG 3:1, CP:SSG 1:1, CP:SSG 1:3) in different concentrations. He evaluate the flow properties of powder and then tablet was prepared by direct compression technique Prepared tablets were evaluated for organoleptic properties, thickness, hardness, friability, disintegration time, wetting time, water absorption ratio, weight variation, percentage drug content, in-vitro dispersion time, uniformity of dispersion and in-vitro dissolution studies. For the results, he forum that the formulation containing CP: SSG 3:1 at a concentration 5% was found to be shows potential results and selected as the optimized formulation. By sublimation technique formulation was prepared and compared with the optimized formulation. At the end, he concluded that the direct compression method is a better alternative to sublimation method. It also concluded that dissolution rate can be enhanced the addition of novel co-processed superdisintegrants which give immediate relief from emesis (Chacko et al. 53-56).

5. Gudas G. K. et al formulated the Promethazine HCl fast dissolving tablets using five different superdisintegrants that were sodium sodium starch glycolate, crosipovidone, croscarmellose, L-HPC and pregelatinised starch. Powder blend was evaluated for flow properties. That the tablet was evaluated for parameter like hardness, friability, disintegration time, dissolution rate etc. The prepared tablets were found as per pharmacopeial limit. He concluded that the formulation congaing crosipovidone, mannitol and microcrystalline cellulose gave fast disintegration and higher drug release (Gudas et al. 867-71).
6. Haware R.V. et al developed mouth melt tablet of Promethazine HCl. Taste-masked granules were prepared using Eudragit®E100 by extrusion. Tablets were prepared by direct compression. The increased dissolution rate was due to the reduced crystallinity. The formulated tablets were disintegrated within 15 s. Tablets with Ac-Di-Sol (4%) showed complete release within 1 min, while marketed conventional tablets release 25% during the same period. The stability study indicate increase in in-vitro disintegration time, tensile strength and decrease in friability and water absorption ratio was found (Haware et al. 1006-15).

7. Kolhe s. et al developed the fast disintegrating tablet of Promethazine HCl. The taste making was done by the Eduragit E100 with solvent evaporating methods. The taste masking was evaluated by time intensity method. In the tablet formulation camphor was sued as subliming agent, SSG and crospovidone was used as super disintegrant. Tablets were evaluated as per pharmacopoeial test. Researcher found that the taste masking is obtained for prepared tablets. There was not any effect of pH on drug dissolution. By in-vivo study on healthy volunteers confirm the taste making of formulation (Kolhe, Ghadge and Dhole 1-11).

8. Manivannan and Kante developed mucoadhesive buccal tablets containing promethazine hydrochloride. Tablets were prepared using polymers such as Carbopol 934P, HPMC K4M and Chitosan in varying concentration by direct compression technique. The Prepared tablets were evaluated for thickness, hardness, friability, and weight variation, uniformity of content, surface pH study, In-vitro swelling study, matrix erosion study, In-vitro bioadhesion study, ex-vivo mucoadhesion time, in-vitro drug release study and stability study. The surface pH of all tablets was found to be near to buccal pH, hence it can predict no irritation would observe with these tablets. The formulation containing carbopol 934P and HPMC K4M in the ratio (1:1) showed good bioadhesive force and maximum drug release of 96.62% for 10 hours. It was observed that the optimized formulation follows korsmeyerpeppas release kinetics. The optimized formulation was found to be stable upon conducting stability studies as per ICH guidelines (Manivannan and Kante 706-17).
9. James L. Ford et al studied the effects of formulation variables on the release rates of promethazine hydrochloride from hydroxyl propyl methyl cellulose (HPMC) tablet. The major controlling factor appeared to be the promethazine: HPMC ratio and a straight-line relationship existed between the Higuchi-type release rate and the reciprocal of the tablet content of HPMC. Change of the particle size range of promethazine from 45–63 to 500–700 μm, there was just 12% increase in the drug release rate. The lowest viscosity grade of HPMC gave the highest release rates at constant HPMC: drug ratio. The other grade of HPMC gave the similar type of drug release (Ford, Rubinstein and Hogan 327-38).

10. Shah et al prepared fast dissolving sublingual film of Promethazine HCl using HP β-CD. Fast dissolving sublingual film (FDSF) was formulated using pullulan and propylene glycol (PG) by solvent casting method. Complete taste masking was successfully obtained with HP β-CD, aspartame and grape fruit flavour. Complex of drug was proved using FTIR, DSC and XRD studies. Optimization of concentration of pullulan and PG was done using $3^2$ full factorial design. Batches were evaluated for the parameters like elongation, tensile strength, folding endurance and in vitro disintegration studies. In vitro dissolution indicated 100 % drug release within 7.5 min. Scanning electron microscopy studies also showed uniform drug distribution and integrity of film. In vivo sublingual absorption in human indicated that 70 % of drug absorbed in 10 min. at the end it was concluded that the develop formulation of PMZ HCl will give faster onset of action and avoid unnecessary drug intake leading to traveller friendly formulation (Shah, Shah and Mehta 91-99).

11. Shivhare U.D. et al developed the transdermal film of PMZ- HCl with combination of Eudragit RS & RL 100. Dimethyl sulphoxide and Dibutyl phthalate were utilized as a skin permeation enhancer and a plasticizer, respectively. The prepared transdermal films were evaluated for thickness, folding endurance, weight variation, flatness, moisture absorption, moisture loss, moisture content, water vapor transmission, drug contain uniformity and in vitro permeation study. Drug polymer interactions were determined by FTIR. In vitro drug release study was performed by using Franz-diffusion cell. The transdermal films prepared by using Eudragit RS 100 and Eudragit RL 100 showed good physical properties. The batch F5 containing Eudragit RL 100:
Eudragit RS 100 with ratio of 5:1 showed maximum drug release (96.15%) and showed fickian diffusion (Dahodwala and Sheikh 559-65).

12. McDonough J. A. et al Developed the Microcapsule-gel formulation of promethazine HCl for controlled nasal delivery. Intra-nasal delivery is considered a feasible alternative route for administration of medications to treat space motion sickness. A controlled-release microencapsulated dosage formulation was developed using spinning disk atomization and release rates for the PMZ HCl microcapsules were determined in phosphate buffered saline. An animal study was conducted to determine the irritation response of rat nasal mucosa when dosed with encapsulated and non-encapsulated PMZ HCl (McDonough et al. 109-16).

13. Patel D.M. et al developed the oral dissolving film of PMZ-HCl. As per the area of petriplate drug amount was calculated. Film was made using different grade of HPMC (E3, E5, E15 and E50) by solvent casting method. The effect of different plasticizers like PEG 200, PEG 400, PEG 600, glycerine, propylene glycol, triethylcitrate were use to evaluate physicomechanical properties of casted films. FTIR spectral studies showed to check interaction between drug and excipients. Formulation was optimized by experimental design and evaluated for in vitro dissolution characteristics, in vitro disintegration time and their physic-mechanical properties. The optimized formulation containing HPMC E15 and PEG 400 showed greater drug dissolution i.e. more than 95% within 10 min, satisfactory in vitro disintegration time (18 sec) and with good physic-mechanical properties. The stability study of optimized formulation for 1 month showed no appreciable change in drug content, in vitro drug release and in vitro disintegration time (Patel and Dabhi 4728-40).

14. Sindhu A. et al developed the fast dissolving sublingual wafers of PMZ HCl. Taste masking was done by inclusion complexation with β-Cyclodextrin, confirmed by e-tongue evaluation. The wafers were prepared by lyophilization, with t polye help of different polymers like Gelatin, Xanthan gum and Methyl cellulose in different ratios. Results of developed film was satisfactory when tested for uniformity of weight, thickness, surface pH, uniformity of drug content, disintegration time, moisture uptake,
moisture loss, moisture content, and in vitro drug release studies. Ex vivo drug permeation studies were carried out using porcine membrane model and which was 33-99% within 6 min and in vitro release 98-100% within 6 min. The combination of Gelatin and Xanthan gum gave the maximum drug release. There was no any change in drug content, surface pH, and in vitro drug release and ex vivo permeation after 8 weeks stability studies. By that it was concluded stable and fast disintegrating Promethazine HCL lyophilized sublingual wafers with good compatibility was formulated (Ganguly et al. 71-92).

15. Pathak K et al formulated promethazine theoclate-loaded solid lipid nanoparticles (SLN). The SLNs prepared by the solvent injection method were optimized by central composite design. The compitol 888 ATO as lipid, poloxamer 407 as surfactant and isopropyl alcohol as solvent was used to prepared SLN. The results obtain by software analysis, formulation F7 with a particle size of 266.2 ± 1.39 nm, entrapment efficiency of 89.60 ± 0.15% and cumulative release of 90.26 ± 1.18% was selected as the optimized formulation. The drug release was followed Higuchi model which indicating diffusion as the mechanism of drug release. Transmission electron microscopy revealed spherical nanoparticles of optimized batch. A high recrystallization index of 76.95% indicates less chance for SLNs to undergo polymorphism and can be signified as stable formulation (Kumar et al. 279-86).

16. Manivannan. R et al developed promethazine hydrochloride buccal tablets. Carbopol 934P, HPMC K4M and Chitosan in different concentration were used to make table by direct compression technique. The surface pH of all tablets was found to be near to buccal pH so it was concluded there was not irritation. The formulation containing carbopol 934P and HPMC K4M in the ratio (1:1) showed good bioadhesive force and maximum drug release of 96.62% for 10 hours. It was observed that the optimized formulation follows korsmeyer-peppas release kinetics (Manivannan and Kante 706-17).
2.6 Literature for Diphenhydramine HCl

1. Lavande J.P. et al formulated orodispersible tablets of Diphenhydramine HCl. Results obtained were suggested that the tablets of all formulations have acceptable physical parameters and also there was no incompatibility between drug and excipients. The \textit{In vitro} release of drug from optimized batch formulation was quick when compared to other formulations. Stability study carried out as per ICH guidelines for three months and results revealed that upon storage disintegration time of tablets had not shown any significant difference. Finally it was concluded that the stable orodispersible tablets of DPH can be developed for the rapid release of drug (Lavande et al. 21-28).

2. Gowtham.M et al developed fast dissolving tablet of DPH HCl. The tablets were prepared by direct compression method. Fast disintegration was obtained by pregelatinized starch, crosspovidone and SSG as superdisintegrants. Powder was evaluated for flow properties. The tablets were evaluated for disintegration time and drug release. The optimized batch gave the disintegration time 35 sec. and drug release 81.04%. This batch contained the SSG at concentration of 5%. The direct compression method was best and less time consuming method for tablet preparation with cost effectiveness (Gowtham et al. 309-19).

3. Sanna et al formulated the different types of topical formulation of DPH HCl. Microemulsion (A), microemulsion+silica (B), Na Alginate emulg gel (C), Carbopol cream (D) and hydroxyethylcellulose gel (E) was prepared for drug topical release. The skin irritation potential and the formulation effect on skin reaction induced by histamine were investigated \textit{in vivo}. Developed formulations were compared with commercial cream of DPH (Allergan®). The diffusion rate values showed the rank order E > A > B > C > D > Control, and all prepared formulations are able to improve the diffusion of drug compared with commercial cream. From the prepared formulations, the hydroxyethylcellulose gel and microemulsions appear to be the most efficient vehicles in promoting the drug release. \textit{In vivo} studies suggested that there was not skin irritation and determine a reduction of the response induced by histamine suggesting that their potential use as alternative topical dosage forms for effective local antihistaminic therapy (Sanna, Peana and Moretti 863-69).
4. Margret Chandira et al developed DPH HCl gel caps. The Rapid Release gelcaps were prepared by direct compression method using pregelatinised maize starch and croscarmellose sodium in different concentrations. The granules showed satisfactory flow properties and compressibility. All the formulations showed acceptable pharmacopoeial standards. The result of formulation B8 with contain 40 mg Pregelatinised maize starch and 12 mg Croscarmellose sodium gave rapid release of DPH HCl. Successful formulation was found stable after evaluation for physicochemical parameters when kept for 30 days at room temperature, 40°C ± 2 & 75 % RH and 2-8°C. It concluded that gel caps containing DPH HCl, 40 mg pregelatinised maize starch and 12 mg croscarmellose sodium provide a promising results (Chandira et al. 1-10).

5. Fakhry and Hassan developed topical formulations of DPH HCl. In developed novel drug preparations for topical delivery through the skin, the choice of vehicle formulations for a given drug can very much persuade the rate and extent of drug permeation across the skin. Required amount of each base was placed in the dissolution basket apparatus, which was covered with the skin of a rat to simulate the percutaneous absorption, and the amount of drug released through the rat skin in the dissolution media, was measured. The different bases of diphenhydramine have shown different release rate but for them the gel base shown the highest drug release (Fakhry and Hassan 1-15).

6. Shahi S. et al developed liposomal formulation of DPH HCl for topical delivery. The optimized formulation showed the sustained release action as compared to drug solution. Drug entrapment increased with the increase in the concentration of soya lecithin and cholesterol. The prepared gel formulations were studied for their in vitro release characteristics through guinea pig skin and showed sustained release action for 8 h when compared with plain gel. It was concluded that developed formulation liposomal gel was the stable with respect to the parameters selected (Shahi et al. 534-42).
7. Ishikawa et al made oil in water lotion (emulsion lotion EL) for control release of DPH. 2-methacryloyloxyethyl phosphorylcholine n-butyl methacrylate copolymer (PMB) as an emulsifier that provides controlled-release was developed. Formulation with 5% DPH, 5% soybean oil, and 4% PMB in water was made by a high-pressure homogenizer. Polysorbate 80 (TO) was used instead of PMB for comparison. For stripped skin, penetration of DPH from 4% PMB EL was slower than that from 1% TO EL where as results for intact skin was similar. The same results were also obtained in vivo study of rabbit skin. When 4% PMB EL dried on the skin, it made a thin film matrix incorporating the oil phase, which controlled the release of DPH. The release rate could be controlled by the ratio of oil phase to PMB. The EL with PMB shows promise as a vehicle for long-acting treatment of skin diseases (Ishikawa et al. 16-22).

8. Ogbonna et al formulated sustained release tablet using Colocasia antiquorum gum (CAG) for diphenhydramine HCl and theophylline hydrate. The gum showed a fine bland, tasteless, brownish white powder with poor aqueous solubility in water; with presence of starch and saponin. Form the all the formulations T2 batch containing 16.67 % of the CAG in theophylline sustained release for 8 h making it a suitable binder for formulations at this concentration and mixed results in the dissolution profile of the two drugs in their mechanism and kinetics of release (Ogbonna et al. 519-24).

9. Akkaramongkolporn et al studied the effect of cationic resin on drug release of DPH HCl using methocel K4M or Ethocel 7cP as Matrix Formers. HPMC- and EC-based matrices with varying amounts (0–40%w/w) of resin incorporation were prepared by a direct compression. Prepared tablets were evaluated for hardness, friability; surface morphology and drug release were evaluated. The friability of HPMC-based matrices increased with increasing the amount of resin, corresponding to their decreased hardness. In contrast, the EC-based matrices showed no significant change in friability in spite of decreasing hardness. Drug release was influenced by incorporated resin differently from HPMC and EC based matrices in deionized water. The resin further retarded DPH release from HPMC-based matrices due to the gelling property of HPMC and the ion exchange property of the resin. In contrast, the release from EC-based matrices initially increased because of the disintegrating property of the resin, but
thereafter declined due to the complex formation between released drug and dispersed resin via the ion exchange process. It was concluded that the use of resin could alter the release and physical properties of formulation (Akkaramongkolporn et al. 899-908).

10. Kiran Bhise et al explored the passive and electrically assisted transdermal transport of DPH by iontophoresis. For better bioavailability, better patient compliance, and enhanced delivery of DPH, an iontophoretic drug delivery system of a thermosensitive DPH gel was formulated using Lutrol F-127. The effects of pH, polymer concentration, electrode design, and pulse rate on the DPH permeation were investigated. The relationship between temperature, viscosity, and conductance of DPH was correlated using conductometry. Iontophoretic transport of DPH was found to increase with a decrease in the pH of the medium and an increase in the surface area of the electrode. Viscosity measurements and flux calculations indicated the suitability of the Lutrol gel for transdermal iontophoretic delivery of DPH. Anodal pulsed iontophoresis with disc electrode significantly increased the DPH skin permeation as compared with the passive controls (Kotwal, Bhise and Thube 320-25).

11. Patel D. M. et al formulated lozenges to meet the need of improved bioavailability by avoiding hepatic first pass metabolism of the drug. The lozenges were formulated using various sugars like mannitol, dextrose, sucrose and isomalt. Polyethylene glycol 200, propylene glycol and glycerine were tested as plasticizer in formulation. The prepared formulations were subjected to various evaluation parameters. After completion of stability study for a period of 1 month, the optimized formulation was subjected to evaluation parameters. Lozenges formulated using isomalt and 0.1 ml glycerine remained as hard candy, while lozenges were not formed with any other sugar. The optimized formulation showed a desired hardness, content uniformity of 97 % and drug release more than 99 % within 20 min. After stability study, it was found that the lozenges were not altered in terms of above parameters and were stable (Patel et al. 822-34).

12. Wang et al evaluated effect of the effect of block structure and plasticizer on drug release from DPH patch. Three drugs, methyl salicylate, capsaicin, and
diphenhydramine hydrochloride are selected as model drugs. The FTIR, DSC, and wide-angle XRD test had shown a good compatibility between drugs and matrices. In addition, atomic force microscopy and rheological studies of the formulations were performed to explore the effect of SIS structure and plasticizer on drug release behaviors. For methyl salicylate and capsaicin, drug diffusion in the PSA matrices is the main factor controlled by the release kinetic constant k. But for water-soluble drugs such as DPH HCl, the release rate is governed by water penetration with the competition from diffusion mechanisms (Wang et al. 556-67).

13. Angela Y. Lin et al studied effect of the crystallization of the endogenous surfactant nonoxynol 100 in Eudragit NE30D-free films Because the phase transition of nonoxynol 100 in Eudragit NE30D occurred at ambient conditions, its influence on the dissolution of diphenhydramine HCl pellets coated with Eudragit NE30D was studied. The results showed the dissolution rate increased as the level of nonoxynol 100 increased in the coating formula. Compared to the commonly used water-soluble additive human peripheral mononuclear cell, nonoxynol 100 was more effective in enhancing the dissolution of diphenhydramine HCl from pellets coated with Eudragit NE30D. Further study showed that the phase separation of the surfactant during aging tends to stabilize or slightly increase dissolution rates at higher surfactant levels (Lin et al. 57-68).

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