CHAPTER 4

MATERIALS AND METHODS

4.1 MATERIALS

Table 4.1: List of drug and suppliers

S.No	Drug	Supplier
1	Loratadine (Micronised)	Rolabo, SL, Spain
2	Loratadine (Micronised)	Matrix Labs, India
3	Phenylephrine HCl	Divi‘s Lab, India

Table 4.2: List of chemicals and suppliers

S.No	Chemicals	Supplier
1	Isopropyl alcohol	SD Fine chemicals, Mumbai
2	Acetone	SD Fine chemicals, Mumbai
3	Methanol	Merck India Limited ,Mumbai
4	Hydrochloric Acid	SD Fine chemicals, Mumbai
5	Acetic acid	Merck India Limited ,Mumbai
6	Sodium Acetate	Merck India Limited ,Mumbai
7	Potassium dihydrogen phosphate	Merck India Limited ,Mumbai
8	Sodium hydroxide	Merck India Limited, Mumbai
9	Monobasic sodium phosphate	Merck India Limited, Mumbai
10	Anhydrous dibasic sodium phosphate	Merck India Limited, Mumbai

Table 4.3: List of excipients used in formulation

S.No	Excipient	Supplier
1	Hydroxypropyl methyl cellulose	Dow chemicals
2	Povidone	ISP, Mumbai
3	Microcrystalline cellulose	FMC polymer, Mumbai
4	Magnesium stearate	Ferro Portugal
5	Kollidon VA 64	BASF, Mumbai
6	Avicel CE 15	FMC polymer, Mumbai
7	Pearlitol flash	Roquette, France
8	Mannitol (Pearlitol 200SD)	Roquette, France
9	Croscarmelose Sodium (Ac-Di-Sol SD-711)	FMC polymer, Mumbai
10	Aspartame	Manus Aktteva, India
11	Raspberry flavour	Givaudan UK Ltd
12	Lactose monohydrate	DMV
13	Sodium lauryl sulphate	DKSH India, Mumbai
14	Starch 1500 LM	Colorcon,
15	Citric acid (Anhydrous)	Kinsun International China
16	Colloidal silicon dioxide	Cabot Sanmar Ltd India,
17	Starch	Roquette, France

Table 4.4: List of Equipments

S.No.	Name of the Equipment	Model	Supplier
1	Mechanical stirrer	RQ-127A	REMI
2.	Electronic weighing balance	SB8000	Mettler Toledo
3.	Disintegration	ED-2L	Electrolab
4.	Friabilator	EL-2D	Electrolab
5.	Hot air oven	-	Heraeus,Germany
6.	Compression machine	CMD4	Cadmach
7.	Stability chamber	TH 238G	Thermolab
8.	Tablet hardness tester	8M	Dr.Schleuniger
9.	Induction cap sealer	CSP 300	Sigma Jr
10.	UV-Shimadzu	UV-2450(PC)S	Shimadzu
11.	Quadro co- mill	197	Gansons
12.	Sieves	-	Retsch
13.	DSC	822	Mettler Toledo
14.	Dissolution apparatus	2000 USP	LABINDIA
15.	Vernier calipers	CD-6‖CSX	Mitutoyo, Japan
16.	Tap density meter	ETD-1020	Electro lab
17.	pH-Meter	5Star	Thermo orion
18.	Rapid dryer	7G200	Retsch

Hydroxypropyl methyl cellulose

Non-proprietary Names	BP: Hypromellose JP: Hydroxypropylmethylcellulose PhEur: Hypromellosum USP: Hypromellose
Synonyms	Benecel MHPC; E464; hydroxypropyl methylcellulose; HPMC; Methocel; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose; Metolose; Tylopur.
Description	Hypromellose is an odorless and tasteless, white or creamy white fibrous or granular powder.
Functional categories	Coating agent; film-former; rate-controlling polymer for sustained release; stabilizing agent; suspending agent; tablet binder; viscosity-increasing agent.
Solubility	Soluble in cold water, forming a viscous colloidal solution; practically insoluble in chloroform, ethanol(95%), and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane, and mixtures of water and alcohol. Certain grades of hypromellose are soluble in aqueous acetone solutions, mixtures of dichloromethane and propan-2-ol, and other organic solvents
Melting point	It browns at 190–200^{0}C; chars at 225–230^{0}C.Glass transition temperature is 170–180^{0}C.
Stability and storage conditions	Hypromellose powder is a stable material, although it is hygroscopic after drying. Solutions are stable at pH 3–11. Increasing temperature reduces the viscosity of solutions. Hypromellose powder should be stored in a well-closed container, in a cool, dry place.
Incompatibilities	Hypromellose is incompatible with some oxidizing agents.
Applications	It is used for extended-release formulations and enhances the aqueous solubility of poorly soluble compounds by making solid dispersions.

Povidone

Non-proprietary Names	BP: Povidone, JP: Povidone, PhEur: Povidonum USP: Povidone
Synonyms	E1201; Kollidon; Plasdone; poly[1-(2-oxo-1-pyrrolidinyl)ethylene]; polyvidone; polyvinylpyrrolidone; PVP; 1-vinyl-2-pyrrolidinone polymer
Empirical formula	$(C_6H_9NO)_n$
Molecular weight	2500–3 000 000 g/mol
Description	Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder.
Functional categories	Disintegrant; dissolution aid; suspending agent; tablet binder.
Solubility	Freely soluble in acids, chloroform, ethanol (95%), ketones, methanol, and water;
Melting point	Softens at 150°C.
Stability and storage conditions	Povidone may be stored under ordinary conditions without undergoing decomposition or degradation. However, since the powder is hygroscopic, it should be stored in an airtight container in a cool, dry place.
Incompatibilities	It forms molecular adducts in solution with sulfathiazole, sodium salicylate, salicylic acid, phenobarbital, tannin, and other compounds.
Applications	Povidone solutions may also be used as coating agents and it is also used as a suspending, stabilizing, or viscosity-increasing agent .

Microcrystalline cellulose

Non-proprietary Names	BP: Microcrystalline cellulose, PhEur: Cellulosemmicrocristallinum, JP: Microcrystalline cellulose, USPNF: Microcrystallinecellulose
Synonyms	Avicel PH; Cellets; Celex; cellulose gel; hellulosummicrocristallinum; Celphere; Ceolus KG; crystalline cellulose; E460; Emcocel; Ethispheres; Fibrocel; MCC Sanaq; Pharmacel; Tabulose; Vivapur.
Empirical formula	$(C_6H_{10}O_5)_n$ where n~220
Molecular weight	3600 g/mol.
Description	It occurs as a white, odorless, tasteless, crystalline powder composed of porous particle.
Functional categories	Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant
Solubility	Slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents.
Melting point	260-270^{o}C
Loss on drying	≤7.0%
Stability and storage conditions	Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place
Incompatibilities	Microcrystalline cellulose is incompatible with strong oxidizing agents
Applications	Microcrystalline cellulose is widely used primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct compression processes.

Magnesium stearate

Non-proprietary Names	BP: Magnesium Stearate, JP: Magnesium Stearate , PhEur: Magnesium Stearate , USP-NF: Magnesium Stearate
Synonyms	Dibasic magnesium stearate; magnesium distearate; magnesiistearas; magnesium octadecanoate; octadecanoic acid, magnesium salt; stearic acid, magnesium salt; Synpro 90
Empirical formula	$C_{36}H_{70}MgO_4$
Molecularweight	591.24 g/mol.
Description	Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.
Functional categories	Tablet and capsule lubricant.
Solubility	Practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%).
Melting point	117–150 ^{o}C
Density	1.092 g/cm3
Loss on drying	46.0%
Stability and storage conditions	Magnesium stearate is stable and should be stored in a well-closed container in a cool, dry place.
Incompatibilities	Incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials.
Applications	It is primarily used as a lubricant in capsule and tablet manufacture.

Kollidon VA 64

Non-proprietary Names	Graft co polymer ,Copovidone ,Copolyvidone
Molecular weight	45 000 – 70 000g/mol
Description	Kollidon VA 64 is a graft copolymer of 1-vinyl-2-pyrrolidone and vinyl acetate in a ratio of 6:4 by mass., white or slightly yellowish, free-flowing powders with a faint characteristic odor and practically no taste.
Functional categories	It is used in film casting, as dry binder in direct compression and as granulating, retarding and film-forming agents.
Solubility	It is soluble in water. It is also soluble in acetone, methanol, ethanol and dimethylformamide less soluble in ether, aliphatic and alicyclic compounds
Glass transition temperature	Approximately 105^0c
Stability and storage conditions	It should be closed in tightly closed container. Becomes sticky when exposed to air due to moisture absorption
Applications	Kollidon VA 64 is used in Direct compression. Roller compaction

Mannitol SD 200

Non-proprietary Names	JP: D-Mannitol ,PhEur: Mannitolum ,USPNF: Mannitol
Synonyms	Cordycepic acid; *C*PharmMannidex*; E421; manna sugar; D-mannite; mannite; *Mannogem*;*Pearlitol*
Empirical formula	$C_6H_{14}O_6$
Molecular weight	182.17 g/mol
Description	Mannitol is D-mannitol. It is a hexahydric alcohol related to mannose and is isomeric with sorbitol. Mannitol occurs as a white, odorless, crystalline powder, or free-flowing granules.
Functional categories	Diluent; diluent for lyphilized preparations; sweetening agent; tablet and capsule diluent ,tonicity agent
Solubility	Freely soluble in water.
Stability and storage conditions	Mannitol is stable in the dry state and in aqueous solutions. Solutions may be sterilized by filtration or by autoclaving
Incompatibilities	Mannitol solutions, 20% w/v or stronger, may be salted out by potassium chloride or sodium chloride.
Application	In pharmaceutical preparations it is primarily used as a diluent (10–90% w/w) in tablet formulations, Mannitol may be used in direct-compression tablet applications, for which the granular and spray-dried forms are available, or in wet granulations. It is also used as a diluent in rapidly dispersing oral dosage forms

Lactose Monohydrate

Non-proprietary Names	BP: Lactose monohydrate PhEur: Lactosum monohydricum JP: Lactose USPNF: Lactose monohydrate
Synonyms	Lactochem Crystals, Lactochem Fine Crystals
Empirical formula	$C_{12}H_{22}O_{11}\cdot H_2O$
Molecular weight	360.31 g/mol
Description	Lactose occurs as white to off-white crystalline particles or powder. Lactose is odorless and slightly sweet-tasting; α-lactose is approximately 20% as sweet as sucrose, while β-lactose is 40% as sweet.
Functional categories	Binding agent; diluent for dry-powder inhalers; tablet binder; tablet and capsule diluent.
Solubility	It is soluble in water and insoluble in Chloroform, Ethanol and ether
Stability and storage conditions	Mold growth may occur under humid conditions (80% relative humidity and above). Lactose may develop a brown coloration on storage, the reaction being accelerated by warm, damp conditions, stored in a well-closed container in a cool, dry place
Incompatibilities	A Maillard-type condensation reaction is likely to occur between lactose and compounds with a primary amine group to form brown, or yellow-brown-colored products
Applications	Anhydrous lactose is widely used in direct compression tabletting applications and as a tablet and capsule filler and binder. Anhydrous lactose can be used with moisture-sensitive drugs due to its low moisture content

Aspartame

Non-proprietary Names	BP: Aspartame PhEur: Aspartame USP-NF: Aspartame
Synonyms	(3S)-3-Amino-4-[[(1S)-1-benzyl-2-methoxy-2-oxoethyl]amino]-4-oxobutanoic acid; 3-amino-N-(a-carboxyphenethyl)succinamic acid N-methyl ester; 3-amino-N-(a-methoxycarbonylphenethyl)succinamic acid; APM; aspartamum; aspartyl phenylamine methyl ester; Canderel; E951; Equal; methyl NL-a-aspartyl-L-phenylalaninate; NatraTaste; NutraSweet; Pal Sweet; Pal Sweet Diet; Sanecta; SC-18862; Tri-Sweet.
Empirical formula	$C_{14}H_{18}N_2O_5$
Molecular weight	294.30g/mol
Description	Aspartame occurs as an off white, almost odorless crystalline powder with an intensely sweet taste.
Solubility	Slightly soluble in ethanol (95%); sparingly soluble in water.
Stability and storage conditions	Aspartame is stable in dry conditions. Stability in aqueous solutions has been enhanced by the addition of cyclodextrins, and by the addition of polyethylene glycol 400 at pH 2. The bulk material should be stored in a well-closed container, in a cool, dry place.
Incompatibilities	Aspartame is incompatible with dibasic calcium phosphate and also with the lubricant magnesium stearate. Reactions between aspartame and sugar alcohols are also known.

Croscarmellose sodium

Non-proprietary Names	BP: Croscarmellose Sodium JP: Croscarmellose Sodium PhEur: Croscarmellose Sodium USP-NF: Croscarmellose Sodium
Synonyms	Ac-Di-Sol; carmellosum natricum conexum; crosslinked carboxymethyl cellulose sodium; Explocel; modified cellulose gum; Nymcel ZSX; Pharmacel XL; Primellose; Solutab; Vivasol.
Description	Croscarmellose sodium occurs as an odorless, white or grayish white powder.
Functional categories	Tablet and capsule disintegrant.
Solubility	Insoluble in water, although rapidly swells to 4–8 times its original volume on contact with water. Practically insoluble in acetone, ethanol and toluene.
Stability and storage conditions	It is a stable though hygroscopic material.A model tablet formulation prepared by direct compression,with croscarmellose sodium as a disintegrant, showed no significant difference in drug dissolution after storage at 30ºC for 14 months.It should be stored in a well-closed container in a cool, dry place.
Incompatibilities	Croscarmellose sodium is not compatible with strong acids or with soluble salts of iron and some other metals such as aluminum, mercury, and zinc.
Applications	Croscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant for capsules, tablets, and granules.

Sodium lauryl sulphate

Non-proprietary Names	BP: Sodium Lauryl Sulphate JP: Sodium Lauryl Sulfate PhEur: Sodium Laurilsulfate USP-NF: Sodium Lauryl Sulfate
Synonyms	Dodecyl alcohol hydrogen sulfate, sodium salt; dodecyl sodium sulfate; dodecylsulfate sodium salt; Elfan 240; lauryl sodium sulfate; lauryl sulfate, sodium salt; monododecyl sodium sulfate; natrii laurilsulfas; sodium dodecyl sulfate; sodium n-dodecyl sulfate; sodium laurilsulfate; sodium monododecyl sulfate; sodium monolauryl sulfate; SDS; SLS; sulfuric acid monododecyl ester, sodium salt; Texapon K12P.
Empirical formula	$C_{12}H_{25}NaO_4S$
Molecular weight	288.38 g/mol
Description	Sodium lauryl sulfate consists of white or cream to pale yellow colored crystals, flakes, or powder having a smooth feel, a soapy, bitter taste, and a faint odor of fatty substances.
Functional categories	Anionic surfactant; detergent; emulsifying agent; skin penetrant; tablet and capsule lubricant; wetting agent.
Solubility	Freely soluble in water, giving an opalescent solution; practically insoluble in chloroform and ether.
Melting point	204 - 207°C.
Stability and storage conditions	It is stable under normal storage conditions. However, in solution, under extreme conditions, i.e. pH 2.5 or below, it undergoes hydrolysis to lauryl alcohol and sodium bisulfate. It should be stored in a well-closed container away from strong oxidizing agents in a cool, dry place.
Incompatibilities	It is incompatible with salts of polyvalent metal ions, such as aluminum, lead, tin or zinc, and precipitates with potassium salts. Solutions of sodium lauryl sulfate (pH 9.5–10.0) are mildly corrosive to mild steel, copper, brass, bronze, and aluminum.
Applications	Sodium lauryl sulfate is an anionic surfactant employed in a wide range of non-parenteral pharmaceutical formulations and cosmetics.

Citric acid

Non-proprietary Names	BP: Citric Acid Monohydrate JP: Citric Acid Hydrate PhEur: Citric Acid Monohydrate USP: Citric Acid Monohydrate
Synonyms	Acidum citricum monohydricum; E330; 2-hydroxypropane-1,2,3-tricarboxylic acid monohydrate.
Empirical formula	$C_6H_8O_7. H_2O$
Molecular weight	210.14 g/mol
Description	Citric acid monohydrate occurs as colorless or translucent crystals, or as a white crystalline, efflorescent powder. It is odorless and has a strong acidic taste. The crystal structure is orthorhombic.
Functional categories	Acidifying agent; antioxidant; buffering agent; chelating agent; flavor enhancer; preservative.
Solubility	Soluble 1 in 1.5 parts of ethanol (95%) and 1 in less than 1 part of water; sparingly soluble in ether.
Melting point	~100ºC (softens at 75ºC)
Stability and storage conditions	Citric acid monohydrate loses water of crystallization in dry air or when heated to about 40ºC. It is slightly deliquescent in moist air.Dilute aqueous solutions of citric acid may ferment on standing. It should be stored in airtight containers in a cool, dry place.
Incompatibilities	Incompatible with potassium tartrate, alkali and alkaline earth carbonates and bicarbonates, acetates, and sulfides and also include oxidizing agents, bases, reducing agents, and nitrates.
Applications	It is used as a flavor enhancer for its tart, acidic taste; as a sequestering agent and antioxidant synergist; component of anticoagulant citrate solutions. Therapeutically, preparations containing citric acid have been used to dissolve renal calculi.

Colloidal silicon dioxide

Non-proprietary Names	BP: Colloidal Anhydrous Silica JP: Light Anhydrous Silicic Acid PhEur: Silica, Colloidal Anhydrous USP-NF: Colloidal Silicon Dioxide
Synonyms	Aerosil; Cab-O-Sil; Cab-O-Sil M-5P; colloidal silica; fumed silica;fumed silicon dioxide; hochdisperses silicum dioxid; SAS; silica colloidalis anhydrica; silica sol; silicic anhydride; silicon dioxide colloidal; silicon dioxide fumed; synthetic amorphous silica;Wacker HDK.
Empirical formula	SiO_2
Molecular weight	60.08 g/mol
Description	Colloidal silicon dioxide is a sub microscopic fumed silica with a particle size of about 15 nm. It is a light, loose, bluish-white-colored, odorless, tasteless, amorphous powder.
Functional categories	Adsorbent; anticaking agent; emulsion stabilizer; glidant; suspending agent; tablet disintegrant; thermal stabilizer; viscosity-increasing agent.
Solubility	Practically insoluble in organic solvents, water, and acids, except hydrofluoric acid; soluble in hot solutions of alkali hydroxide. Forms a colloidal dispersion with water. For aerosil, solubility in water is 150 mg/L at 25ºC (pH 7).
Melting point	1600°C.
Stability and storage conditions	Hygroscopic but adsorbs large quantities of water without liquefying. However, at a pH greater than 7.5 the viscosity increasing properties of colloidal silicon dioxide are reduced; and at a pH greater than 10.7 this ability is lost entirely since the silicon dioxide dissolves to form silicates. The powder should be stored in a well-closed container.
Incompatibilities	Incompatible with diethylstilbestrol preparations.
Applications	Colloidal silicon dioxide is widely used in pharmaceuticals, cosmetics, and food products; improve the flow properties of dry powders in a number of processes such as tabletting and capsule filling.

Starch

Non-proprietary Names	BP: Maize starch; Potato starch; Rice Starch; Tapioca Starch; Wheat Starch JP: Corn Starch; Potato Starch; Rice Starch; Wheat Starch PhEur: Maize Starch; Pea Starch; Potato Starch; Rice Starch; Wheat Starch USP-NF: Corn Starch; Potato Starch; Tapioca Starch; Wheat Starch
Synonyms	Amido; amidon; amilo; amylum; C*PharmGel; Eurylon; fecule; Hylon; maydis amylum; Melojel; Meritena; oryzae amylum; Pearl; Perfectamyl; pisi amylum; Pure-Dent; Purity 21; Purity 826; solani amylum; tritici amylum; Uni-Pure.
Empirical formula	$(C_6H_{10}O_5)_n$
Description	Starch occurs as an odorless and tasteless, fine, white to off-white powder. It consists of very small spherical or ovoid granules or grains whose size and shape are characteristic for each botanical variety.
Functional categories	Tablet and capsule diluent; tablet and capsule disintegrant; tablet binder; thickening agent.
Solubility	Practically insoluble in cold ethanol (96%) and in cold water. Starch swells instantaneously in water by about 5–10% at 37ºC.Starch becomes soluble in hot water at temperatures above the gelatinization temperature. Starches are partially soluble in dimethyl sulfoxide and dimethyl formamide.
Stability and storage conditions	Dry starch is stable if protected from high humidity. Starch solutions or pastes are physically unstable and are readily metabolized by micro-organisms; They should therefore be freshly prepared when used for wet granulation. It should be stored in an airtight container in a cool, dry place.
Incompatibilities	Starch is incompatible with strongly oxidizing substances. Colored inclusion compounds are formed with iodine.
Applications	Starch is a versatile excipient used primarily in oral solid-dosage formulations where it is utilized as a binder, diluent, and disintegrant.

Starch, Pregelatinized

Non-proprietary Names	BP: Pregelatinised Starch PhEur: Starch, Pregelatinised USP-NF: Pregelatinized Starch
Synonyms	Amylum pregelificatum; compressible starch; C*PharmGel; Instastarch; Lycatab C; Lycatab PGS; Merigel; National 78-1551; Pharma-Gel; Prejel; Sepistab ST200; Spress B820; Starch 1500 G; Tablitz; Unipure LD; Unipure WG220.
Empirical formula	$(C_6H_{10}O_5)_n$
Description	Pregelatinized starch occurs as a moderately coarse to fine, white to off-white colored powder. It is odorless and has a slight characteristic taste.
Functional categories	Tablet and capsule diluent; tablet and capsule disintegrant; tablet binder.
Solubility	Practically insoluble in organic solvents. Slightly soluble to soluble in cold water, depending upon the degree of pregelatinization. Cold-water-soluble matter for partially pregelatinized starch is 10–20%.
Stability and storage conditions	Pregelatinized starch is a stable but hygroscopic material, which should be stored in a well-closed container in a cool, dry place.
Applications	Partially pregelatinized starch is a modified starch used in oral capsule and tablet formulations as a binder, diluent, and disintegrant.

Stearic acid

Non-proprietary Names	BP: Stearic Acid JP: Stearic Acid PhEur: Stearic Acid USP-NF: Stearic Acid
Synonyms	Acidum stearicum; cetylacetic acid; Crodacid; Cristal G; Cristal S; Dervacid; E570; Edenor; Emersol; Extra AS; Extra P; Extra S; Extra ST; 1-heptadecanecarboxylic acid; Hystrene; Industrene; Kortacid 1895; Pearl Steric; Pristerene; stereophanic acid; Tegostearic.
Empirical formula	$C_{18}H_{36}O_2$
Molecular weight	284.47 g/mol
Description	Stearic acid is a hard, white or faintly yellow-colored, somewhat glossy, crystalline solid or a white or yellowish white powder. It has a slight odor (with an odor threshold of 20 ppm) and taste suggesting tallow.
Functional categories	Emulsifying agent; solubilizing agent; tablet and capsule lubricant.
Solubility	Freely soluble in benzene, carbon tetrachloride, chloroform, and ether; soluble in ethanol (95%), hexane, and propylene glycol; practically insoluble in water.
Melting point	69-70°C.
Stability and storage conditions	Stearic acid is a stable material; an antioxidant may also be added to it; It should be stored in a well closed container in a cool, dry place.
Incompatibilities	Stearic acid is incompatible with most metal hydroxides and may be incompatible with bases, reducing agents, and oxidizing agents.
Applications	Stearic acid is widely used in oral and topical pharmaceutical formulations. It is mainly used in oral formulations as a tablet and capsule lubricant;it may also be used as a binder or in combination with shellac as a tablet coating. It has also been suggested that stearic acid may be used in enteric tablet coatings and as a sustained-release drug carrier.

Calcium phosphate

Non-proprietary Names	BP: Anhydrous Calcium Hydrogen Phosphate JP: Anhydrous Dibasic Calcium Phosphate PhEur: Calcium Hydrogen Phosphate, Anhydrous USP: Anhydrous Dibasic Calcium Phosphate
Synonyms	A-TAB; calcii hydrogenophosphas anhydricus; calcium monohydrogen phosphate; calcium orthophosphate; Di-Cafos AN; dicalcium ortho phosphate; E341; Emcompress Anhydrous; Fujicalin; phosphoric acid calcium salt (1 : 1); secondary calcium phosphate.
Empirical formula	$CaHPO_4$
Molecular weight	133.06 g/mol
Description	Anhydrous dibasic calcium phosphate is a white, odorless, tasteless powder or crystalline solid. It occurs as triclinic crystals.
Functional categories	Tablet and capsule diluent.
Solubility	Practically insoluble in ether, ethanol, and water; soluble in dilute acids.
Melting point	Does not melt; decomposes at ~425ºC to form calcium pyrophosphate.
Stability and storage conditions	It is a nonhygroscopic, relatively stable material. Under conditions of high humidity it does not hydrate to form the dihydrate. It should be stored in a well-closed container in a dry place.
Incompatibilities	Dibasic calcium phosphate should not be used to formulate tetracyline antibiotics.
Applications	It is used both as an excipient and as a source of calcium in nutritional supplements. It is used particularly in the nutritional/health food sectors. It is also used in pharmaceutical products because of its compaction properties, and the good flow properties of the coarse-grade material.

Iron oxide

Non-proprietary Names	None adopted.
Synonyms	(b) Iron oxide red: anhydrous ferric oxide; anhydrous iron (III) oxide; Bayferrox 105M; CI 77491; diiron trioxide; E172; Ferroxide 212P; Ferroxide 226P; hematite; pigment red 101; red ferric oxide; Sicovit R30.
Empirical formula	Fe_2O_3
Molecular weight	159.70 g/mol
Description	Iron oxides occur as yellow, red, black, or brown powder. The color depends on the particle size and shape, and crystal structure.
Functional categories	Colorant.
Solubility	Soluble in mineral acids; insoluble in water.
Melting point	1565°C.
Stability and storage conditions	Iron oxides should be stored in well-closed containers in a cool, dry place.
Incompatibilities	Iron oxides have been reported to make hard gelatin capsules brittle at higher temperatures when the residual moisture is 11–12%. This factor affects the use of iron oxides for coloring hard gelatin capsules, and will limit the amount that can be incorporated into the gelatin material..
Applications	Iron oxides are widely used in cosmetics, foods, and pharmaceutical applications as colorants and UV absorbers.

Sodium bicarbonate

Non-proprietary Names	BP: Sodium Bicarbonate JP: Sodium Bicarbonate PhEur: Sodium Hydrogen Carbonate USP: Sodium Bicarbonate
Synonyms	Baking soda; E500; Effer-Soda; monosodium carbonate; natrii hydrogenocarbonas; Sal de Vichy; sodium acid carbonate; sodium hydrogen carbonate.
Empirical formula	$NaHCO_3$
Molecular weight	84.01 g/mol
Description	Sodium bicarbonate occurs as an odorless, white, crystalline powder with a saline, slightly alkaline taste. The crystal structure is monoclinic prisms. Grades with different particle sizes, from a fine powder to free-flowing uniform granules, are commercially available.
Functional categories	Alkalizing agent; therapeutic agent.
Solubility	Ethanol (95%) Practically insoluble; ether -practically insoluble; water 1 in 11
Melting point	270°C.
Stability and storage conditions	Sodium bicarbonate is stable in dry air but slowly decomposes in moist air and should therefore be stored in a well-closed container in a cool, dry place.
Incompatibilities	Sodium bicarbonate reacts with acids, acidic salts, and many alkaloidal salts, with the evolution of carbon dioxide. Sodium bicarbonate can also intensify the darkening of salicylates. In powder mixtures, atmospheric moisture or water of crystallization from another ingredient is sufficient for sodium bicarbonate to react with compounds such as boric acid or alum. In liquid mixtures containing bismuth subnitrate, sodium bicarbonate reacts with the acid formed by hydrolysis of the bismuth salt. In solution, sodium bicarbonate has been reported to be incompatible with many drug substances such as ciprofloxacin, amiodarone, nicardipine,and levofloxacin.
Applications	Sodium bicarbonate is generally used in pharmaceutical formulations as a source of carbon dioxide in effervescent tablets and granules. It is also widely used to produce or maintain an alkaline pH in a preparation.

4.2. METHODS

4.2.1. FORMULATION, DESIGN AND EVALUATION OF LORATADINE ORALLY DISINTEGRATING TABLETS

4.2.1.1. Preformulation study

Preformulation involves the application of biopharmaceutical principles to the physicochemical parameters of drug substance are characterized with the goal of designing optimum drug delivery system. Preformulation studies relates to pharmaceutical and analytical investigation carried out proceedings and supporting formulation development efforts of the dosage forms of the drug substance. Preformulation yields basic knowledge necessary to develop suitable formulation. It gives information needed to define the nature of the drug substance and provide frame work for drug combination with pharmaceutical excipients in the dosage form. Hence, the following Preformulation studies were carried out:

I. Test for identification of Loratadine.

1. Physical Appearance
2. Solubility analysis
3. Loratadine - excipients compatibility study

4.2.1.1.1. Physical Appearance

2.0gm of Loratadine powder was taken on a white piece of paper, spreaded the powder and examine visually.

4.2.1.1.2. Solubility studies

Loratadine is sparingly soluble in water. It is freely soluble at pH 1.5 to 2. Increase in the pH drastically changes the solubility of the drug. Loratadine is classified as the Class II according to the Biopharmaceutical Classification of Drugs which means sparingly soluble and highly permeable.(M. Zahirul I. KHAN et al., 2004).

4.2.1.1.3. Drug Excipient compatibility studies

API and excipients were thoroughly mixed in predetermined ratio taken and passed through the sieve no.40. The blend was filled in glass vials and closed with gray rubber stoppers and sealed with aluminium seal and charged in to stress condition at 25ºC/60%RH and 40ºC/75%RH. Similarly API was also kept at all conditions as per the sample the samples were observed for any physical change in 1 month duration.

The drug and the excipients subjected to accelerated stress conditions showed promising results as there was no significant change in the DSC chromatograms of the drug indicating the absence of incompatibility of the drug with the excipients with regard to the excipients present in the formulation and the ratio of drug to excipients designed is shown in Table 4.5.

Table 4.5: Compatibility studies

Sl.NO	INGREDIENTS	RATIO	QUANTITY TAKEN (g)
1	Loratadine (API)	1:0	1
2	API + Mannitol	1:5	0.5 + 2.5
3	API +Cross carmellose sodium (Ac-di-sol SD-711)	1:5	0.5 + 2.5
4	API + Starch 1500 LM	1:0.5	1 + 0.5
5	API + Maltodextrin (Glucidex IT-12)	1:0.5	1 + 0.5
6	API + Citric acid	1:0.25	1 + 0.25
7	API + Colloidal silicon dioxide (Aerosil)	1:0.25	1 + 0.25
8	API + Aspartame	1:0.25	1 + 0.25

4.2.1.1.4. Standard curve for Loratadine using 0.1M phosphate buffer pH 2.0

Accurately weighed 10 mg of Loratadine and it was dissolved in 3 to 5 mL of methanol make up the volume with 0.1M phosphate buffer in a 100 mL volumetric flask, to give a solution of 100 µg/mL concentration of this served as first standard stock solution. From this stock solution 0.4 mL, 0.8 mL, 1.2 mL, 1.6 mL and 2 mL was taken and diluted to 10 mL using 0.1M phosphate buffer pH 2 to get a solution of 4, 8, 12, 16 and 20 µg/mL concentrations. The absorbance of this solution was measured against reagent blank at 281 nm using Shimadzu (UV-1601) spectrophotometer. Standard curve was plotted with concentration on x-axis absorbance on y-axis.

4.2.1.2. FORMULATION OF LORATADINE ORALLY DISINTEGRATING TABLETS

The orally dispersible tablet of Loratadine was prepared using Micro crystalline cellulose as diluent and binder, Pearlitol 200SD as directly compressible diluent, Croscarmellose Sodium as super disintegrant and Starch 1500LM as binder and disintegrant, Maltodextrin (Glucidex IT 12) as diluent, Citric acid as salivating agent, Colloidal silicon dioxide as glidant, Aspartame as sweetener, Mint flavour as flavouring agent, Sodium stearyl fumarate as lubricant.

All ingredients except Colloidal silicon dioxide, Aspartame, Mint flavour, Sodium stearyl fumarate were sifted and mixed in an octagonal blender for 15 minutes. Aspartame, Mint flavour and Colloidal silicon dioxide were sifted and added to above blend and mixed for 5 minutes. Finally the blend was lubricated using Sodium stearyl fumarate and compressed by using 8 mm flat punches with breakline on upper punch and plain on lower punch in Kambert eight station rotary compression machine to produce ODT tablets are shown in Table 4.6.

Table 4.6: Preparation of Loratadine orally disintegrating tablets

Ingredients	Quantity Per Tablet (mg)								
	Trial 001	Trial 002	Trial 003	Trial 004	Trial 005	Trial 006	Trial 007	Trial 008	Trial 009
Loratadine (Micronised)	10	10	10	10	10	10	10	10	10
Pearlitol flash	----	----	----	----	----	----	----	----	103
Mannitol (Pearlitol 200SD)	50	50	55	55	----	40	40	40	----
Maltodextrin (Glucidex IT 12)	----	----	----	----	55	20	20	----	----
Micro crystalline cellulose (Avicel-102)	78.6	77.0	77.5	78	77.5	79	76.5	89.5	20
Croscarmelose Sodium (Ac-Di-Sol SD-711)	12	12	12	12	12	12	12	12	15
Sodium bi-Carbonate	----	----	----	----	----	----	----	----	6
Starch 1500 LM	7	7	7	7	7	----	----	7	----
Citric acid (Anhydrous)	3	1.5	0.5	----	0.5	0.5	0.5	1	3
Colloidal silicon dioxide	2	3	2	2	2	2	3	3	5.2
Strawberry Flavour	----	----	----	----	----	----	----	----	1
Aspartame	4	2	2	2	2	2	2	2	4.8
Mint flavor	0.4	0.5	0.5	0.5	0.5	0.5	0.5	0.5	----
Lubrication									
Sodium stearyl fumarate	3	7	3.5	3.5	3.5	3.5	5	5	2
Tablet weight (mg)	**160**	**163**	**170**	**170**	**170**	**170**	**170**	**170**	**170**

4.2.1.3. EVALUATION OF ODT TABLETS (Gandhi PP *et al*., 2010**)**

The growing importance of orally dispersible tablets was under lined recently when European Pharmacopoeia adopted the term ―Orodispersible tablets‖ and given the limit as 3 min for dispersion in the mouth, when taken orally.

These above formulations being prepared by direct compression method is versatile and simple and very easy to process. The results are very promising with respect to release profiles and disintegration time within limits.

The formulation of orally disintegrating tablets mainly depends on the type of super disintegrants used like Croscarmellose Sodium (Ac-Di-Sol SD-711) and PEARLITOL flash, a combination of Mannitol and Starch used as direct compressible diluent along with Sodium bicarbonate and Citric acid showed good results with 99.98% drug content, 35 Seconds disintegration time, 0.13% friability and 99 % drug release in 10 minutes (Table 4) along with very good mouth feel.

Good hardness was achieved in almost all the formulations. In trial 005 where the increased disintegration time and the wetting time was observed with increased quantity of Maltodextrin .

The compressed tablets showed less weight variation with standard deviation of 1.16 in trial 005 being the maximum amongst all the trials. Weight variation was found to be least in trial 009.

4.2.1.3.1. Friability test (British Pharmacopoeia, Vol.-2, 2007; State Pharmacopoeia-30, 2007**)**

Friability of tablets was determined using Roche Friabilator (Electrolab, Mumbai).The tablets were subjected to the combined effect of abrasions and shock in a Friabilator at 25 rpm and dropping the tablets at a height of six inches in each

revolution. Pre weighed sample of tablets was placed in a Friabilator and subjected to 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. The friability is given by the formula:

$F= (1-W_o/W) X 100$

Where, W_o is the weight of the tablets before the test and W is the weight of the tablet after the test.

%Friability = (Loss in weight / Initial weight) x 100

4.2.1.3.2. Hardness (British Pharmacopoeia, Vol.-2, 2007; United State Pharmacopoeia-30, 2007**)**

Tablet requires a certain amount of strength or hardness and resistance to friability to withstand mechanical shakes of handling in manufacture, packaging and shipping. Hardness generally measures the tablet crushing strength. Changes in hardness result in differences in disintegration and dissolution characteristics. The crushing strength of the tablet was determined using Schleuniger hardness tester.

4.2.1.3.3. Drug content (British Pharmacopoeia, Vol.-2, 2007; United State Pharmacopoeia-30, 2007**)**

Twenty tablets were selected randomly and powdered. A quantity of this powder corresponding to 55 mg of Loratadine was dissolved in 500mL of simulated gastric fluid (SGF) without enzyme, stirred for 60 min and filtered. 10 mL of the filtrate was diluted to 100 mL with SGF without enzyme. Absorbance of this solution was measured using UV spectrophotometer (SHIMADZU 1700) at 278 nm using 0.1N hydrochloric acid as simulated gastric fluid without enzyme as blank and content of Loratadine was estimated.(Fig.2).

4.2.1.3.4. Measurement of wetting time (British Pharmacopoeia, Vol.-2, 2007; United State Pharmacopoeia-30, 2007**)**

A glass petri dish was partially filled with water and a tablet was placed on the surface of a band of filter paper supported on a glass slide. The uptake of water occurred from the lower surface of the tablet. The time required for water to reach the center of the upper surface of the tablet was noted as wetting time.

4.2.1.3.5. Water absorption ratio (British Pharmacopoeia, Vol.-2, 2007; United State Pharmacopoeia-30, 2007**)**

A piece of tissue paper was folded twice and placed in a small petri dish containing 6 mL of water. A tablet was put on the paper and the time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio R, was determined using the following equation:

$$R = 100 \times \frac{W - W}{W}$$

Where W_b is weight of the tablet before absorption and W_a is weight of tablet after water absorption.

4.2.1.3.6. Disintegration time (British Pharmacopoeia, Vol.-2, 2007; United State Pharmacopoeia-30, 2007**)**

The time required for disintegration of six tablets, placed in each tube of disintegration apparatus USP (Electrolab ED-2L), was measured at 37±2°C using 900mL of distilled water.

4.2.1.4. *IN VITRO* DISSOLUTION STUDIES

The tablet samples were subjected to in-vitro dissolution studies using USP Type-I (Basket) dissolution apparatus (LABINDIA DISSO2000) at 37±2°C and 50 rpm speed. As per the official recommendation of USFDA, 900 mL of simulated gastric fluid without enzyme was used as dissolution medium. Aliquot equal to 10 mL was

withdrawn at sampling time of 2, 4, 6, 8,10 minutes and the dissolution media volume was complimented with fresh and equal volume of blank media. The aliquots were filtered and scanned with appropriate dilution and amount of Loratadine released from the tablet samples was determined spectrophotometrically at a wavelength of 278 nm by comparing with the standard calibration curve.

4.2.1.5. STABILITY STUDIES

Selected loratadine orally disintegrating tablets were further subjected to accelerated stability studies upto three months at 40^0C/ 75% RH..The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors, such as temperature, humidity, and light and to establish a retest period for the drug substance or a shelf life for the drug product and recommended storage conditions.(ICH guideline 1996)

4.2.2. FORMULATION DEVELOPMENT AND EVALUATION OF CHEWABLE TABLETS CONTAINING NON- SEDATING ANTIHISTAMINE

4.2.2.1. Preformulation Studies

Preformulation involves the application of biopharmaceutical principles to the physicochemical parameters of drug substance are characterized with the goal of designing optimum drug delivery system. Preformulation studies relates to pharmaceutical and analytical investigation carried out proceedings and supporting formulation development efforts of the dosage forms of the drug substance. Preformulation yields basic knowledge necessary to develop suitable formulation.

It gives information needed to define the nature of the drug substance and provide frame work for drug combination with pharmaceutical excipients in the dosage form. Hence, the following preformulation studies were carried out:

I. Test for identification of Loratadine.

1. Physical Appearance
2. Solubility analysis
3. Loratadine - excipients compatibility study

4.2.2.1.1. Physical Appearance

2.0gm of loratadine powder was taken on a white piece of paper, spreaded the powder and examine visually.

4.2.2.1.2. Solubility studies

Loratadine is sparingly soluble in water. It is freely soluble at pH 1.5 to 2. Increase in the pH drastically changes the solubility of the drug. Loratadine is classified as the Class II according to the Biopharmaceutical Classification of Drugs which means sparingly soluble and highly permeable.(M. Zahirul I. KHAN et al., 2004).

4.2.2.1.3. Drug Excipient compatibility studies

Preformulation studies were carried out for Loratadine and the probable excipients used in the development of this formulation. The Loratadine was mixed with the individual excipient as per the predetermined ratio as given below (table 4.7) and each admixture was filled in glass vial and closed with a rubber stopper and aluminum seal. These vials were charged in stability at Stress condition like 40^0 C / 75 % RH and room temperature of 25^0 C / 60 % RH for a period of one month. Similarly the API was also kept in these two conditions in similar way. The

samples were observed for any physical change in 15 days and in 30 days and the study presented in Table 4.7.

Table 4.7: Drug Excipient compatibility studies

Sl. No	Name of the Ingredient	Ratio
1	Loratadine (API)	1:0
2	API + Lactose Monohydrate (Pharmatose 200)	1:10
3	API + Mannitol (Pearlitol 25C)	1:10
4	API + Maize Starch	1:5
5	API + D & C Yellow	1:0.05
6	API + Citric Acid	1:0.5
7	API + Raspberry flavour	1:0.05
8	API + Aspartame	1:0.5
9	API + Colloidal Silicon dioxide	1:0.5
10	API + Magnesium Stearate	1:0.5

4.2.2.2. Formulation of Loratadine chewable tablets.

Chewable tablets containing Loratadine 5 mg were prepared by selecting the excipients used in pre-formulation studies.

The chewable tablet of Loratadine was prepared by using aqueous wet granulation technique with Micro crystalline cellulose, Lactose Monohydrate and Mannitol as diluents. Ethyl Cellulose as polymer for taste masking. Povidone and Maize starch as binder. Apart from this we have used flavors like Raspberry and Aspartame as Sweetener. Citric acid is used as taste enhancer. Pharma grade colors are used like D&C Yellow No 10, FD&C Yellow No.6 and FD &C Red No 40 as colors. Sodium starch glycolate as disintegrant, Colloidal silicon dioxide and Magnesium stearate as glidant and lubricant respectively (Table 4.8).

Table 4.8: Formulation of chewable tablet (composition)						
Ingredients						
	Trial 001	Trial 002	Trial 003	Trial 004	Trial 005	Trial 006
Loratadine (Micronised)	5	5	5	5	5	5
Micro crystalline Cellulose (Avicel-pH 101)	180	180	----	----	----	-----
Lactose Monohydrate	200	206	335.75	340.75	310.75	161
Mannitol (Pearlitol 25C)	132.75	132.75	150	150	150	350
Ethyl Cellulose (Ethocel Std 10FP)	----	----	25	20	----	---
Micro crystalline cellulose and Guar gum (Avicel-CE 15)	----	----	----	----	50	----
Povidone K-30	10	10	----	----	----	----
Maize Starch	----	----	18	18	18	18
Purified Water	q s	q s	q s	q s	q s	q s
D & C Yellow No 10	1.25	1.25	1.25	----	1.25	---
D & C Red No 40	----	----	----	----	----	1
FD &C Yellow No 6	----	----	----	1.25	----	--
Citric Acid	2	2	2	2	2	2
Raspberry flavour	2.50	2.50	2.50	2.50	2.50	2.5
Aspartame	6	6	6	6	6	5
Sodium starch glycolate	6	----	----	----	----	----
Colloidal silicon dioxide	1.5	1.5	1.5	1.5	1.5	1.5
Magnesium stearate	3	3	3	3	3	4
Tablet weight (mg)	**550**	**550**	**550**	**550**	**550**	**550**

4.2.2.3. Preparation of Granules

Sifting: Sift Loratadine (micronized), Ethyl cellulose, Lactose monohydrate and Mannitol through 40# mesh.

Dry mixing: Load the above materials into Rapid Mixer Granulator (RMG) and mix for 15 minutes at slow speed.

Binder preparation: Dissolve Povidone K 30, and D&C Yellow in purified water. Stir well to dissolve completely.

Preparation of Starch paste: Dissolve Maize starch, and D&C Yellow in small quantity of purified water separately. Stir well to dissolve completely and add both into the required amount of boiled water with continuous stirring. **Granulation**: Add the binder solution / starch paste to the dry mix materials slowly and granulate well.

Drying: Dry the wet mass into Fluidized bed dryer at 60ºC.

Sifting and Milling: Sift the dried granules through 20# mesh. Over sized granules pass through multi mill fitted with 2.0 mm screen, further pass the granules through 20# mesh completely.

Lubrication: Load the sifted granules into blender and add citric acid, Raspberry flavour, aspartame and colloidal silicon dioxide. Mix for 20 min at slow speed. Then add magnesium stearate which is sifted through 60# mesh and Mix for 5 min at slow speed.

Compression: Compress the blend by using 12 mm standard flat punches with plain surface on both sides. The weight, hardness and thickness were adjusted to get uniform tablets by using 8 station tablet compression machine.

4.2.2.3. EVALUATION OF PHYSICAL CHARACTERISTICS OF THE BLEND (Gandhi PP *et al*., 2010**)**

The tablet blends prepared were analyzed for various micrometric and flow properties like bulk density, tapped density, compressibility index, Hauser ratio, angle of repose.

4.2.2.3.1. Bulk density

Bulk density was determined by measuring the volume of a known mass of powder sample that has been passed through a screen into a graduated cylinder *(*USP *Method I*).

Approximately 10gm of test sample, M was introduced into 25 mL dry measuring cylinder without compacting. The powder was levelled carefully without compacting and read the unsettled apparent volume V_0, to the nearest graduated unit. Bulk density was calculated, in g per mL, by the formula.

$(M) / (V_o)$

Generally replicate determinations are desirable for the determination of this property.

4.2.2.3.2. Tapped density

Tapped density was achieved by mechanically tapping a measuring cylinder containing a powder sample. After measuring the initial weight and volume, the cylinder was mechanically tapped, and volume readings were taken until little further volume change is observed.

Procedure: Cylinder containing the sample was tapped mechanically by raising the cylinder and allowing it to drop under its own weight using a suitable mechanical tapped density tester that provides a fixed drop of 14 ± 2 mm at a nominal rate of 300 drops per minute. Unless otherwise specified, the cylinder was tapped 500 times initially and the tapped volume was measured, V_a, to the nearest graduated unit. The tapping was repeated for an additional 750 times and the tapped volume was measured, V_b, to the nearest graduated unit. If the difference between the two volumes is less than 2%, V_b is the final tapped volume, V_f . It was repeated in increments of 1250 taps, as needed, until the difference between succeeding measurements is less than 2%. The tapped density was calculated, in g per mL, by the formula:

$(M) / (V_f)$.

Generally replicate determinations are desirable for the determination of this property.

4.2.2.3.3. Compressibility Index and Hausner's ratio

The *Compressibility Index* and *Hausner Ratio* are measures of the propensity of a powder to be compressed. As such, they are measures of the relative importance of inter particulate interactions. In a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater inter particle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the *Compressibility Index* and the *Hausner Ratio.* T scale of flow ability given in the Table 4.9.

Compressibility Index— Calculate by the formula:

$$CI\ (\%) = 1 - \frac{V_f}{V_o} \times 100$$

Hausner Ratio— Calculate by the formula:

$$HR = \frac{V_f}{V_o}$$

Where V_0 - Bulk volume ; V_f - Tapped volume

Table 4.9: Scale of Flow ability

Compressibility Index (%)	Flow Character	Hausner's Ratio
≤ 10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very Poor	1.46-1.59
> 38	Very, very Poor	> 1.60

4.2.2.3.4. Determination of Angle of Repose:

Angle of repose was determined by using funnel method, the accurately weighed spheres were taken in funnel. The height of funnel was adjusted in such a way that the tip of funnel just touches the apex of heap of blends. The blends were allowed to flow through funnel freely on to surface. The diameter of powder corn was measured, angle of repose was calculated by using following equation.

$$\tan \theta = \frac{h}{r}$$

h = height of pile

θ = angle of repose

r = radius of pile

Table 4.10: Flow properties and corresponding angles of repose

Angle of repose	Flow
$<25^o$	Excellent
$25\text{-}30^o$	Good
$30\text{-}40^o$	Passable
$>40^o$	Very poor

For most pharmaceutical powders, the angle of repose values range form 25 to 45, with lower values indicating better flow characteristics. Values of angle of repose ≤ 30 usually indicate a free flowing material and angle ≥40 suggest a poorly flowing material is shown in Table 4.10.

4.2.2.4. EVALUATION OF CHEWABLE TABLETS (Gandhi PP *et al*., 2010**)**

All the batches of tablets were evaluated for various physical parameters like thickness, weight variation, friability, hardness, drug content and dissolution as per pharmacopoeial standards.

4.2.2.4.1. Thickness (United State Pharmacopoeia-30, 2007**)**

Thickness of tablet is important for uniformity of tablet size. Thickness of tablets can vary with no change in weight because of the difference in the density of the granulation and the pressure applied to the tablets, as well as the speed of the

compression machine. Ten tablets were randomly selected and thickness was measured using vernier calipers and recorded.

4.2.2.4.2. Weight variation (United State Pharmacopoeia-30, 2007**)**

20 tablets were taken and weighed individually on a digital weighing balance. Average weight was calculated and the individual tablet weight was compared to the average. The tablet pass the U.S.P. test if no more that 2 tablets are outside the percentage limit and if no tablet differs by more than double the percentage limit is shown in Table 4.11.

$$\text{Average weight} = \frac{\text{Weight of 20 tablets}}{20}$$

Table 4.11: Weight variation

Average weight of tablet(mg)	**% difference allowed**
130 or Less than	± 10
130-324	± 7.5
More than 324	± 5

4.2.2.4.3. Crushing strength (United State Pharmacopoeia-30, 2007**)**

Tablet requires a certain amount of strength or hardness and resistance to friability to withstand mechanical shakes of handling in manufacture, packaging and shipping. Hardness generally measures the tablet crushing strength. Changes in hardness result in differences in disintegration and dissolution characteristics. The crushing strength of the tablet was determined using Schleuniger hardness tester.

4.2.2.4.4. Friability test

Friability of tablets was determined using Roche Friabilator (Electrolab, Mumbai).The tablets were subjected to the combined effect of abrasions and shock in a Friabilator at 25 rpm and dropping the tablets at a height of six inches in each revolution. Pre weighed sample of tablets was placed in a Friabilator and subjected to 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. The friability is given by the formula:

$F= (1-W_o/W) X 100$

Where, W_o is the weight of the tablets before the test and W is the weight of the tablet after the test.

%Friability = (Loss in weight / Initial weight) x 100

4.2.2.4.5. Content uniformity test (United State Pharmacopoeia-30, 2007)

Ten tablets from each formulation were powdered. The powdered sample equivalent to 100 mg of drug was transferred to a volumetric flask and dissolved in methanol, mixed and filtered. Required amount of phosphate buffer pH 7.4 was added to the filtrate, suitably diluted with media and drug content was analyzed against blank by UV spectrophotometer at 278 nm. The percentage of drug present in the tablets was calculated.

4.2.2.5. *IN VITRO* DISSOLUTION STUDIES

The tablet samples were subjected to in-vitro dissolution studies using USP Type-II(Paddle) dissolution apparatus (LABINDIA DISSO2000) at 37±2°C and 50 rpm speed. As per the official recommendation of USFDA, 900 mL of 0.1 N HCl

was used as dissolution medium. Sampling (5 ml) was at done 15, 30, 45 and 60 min and it was replaced with equal volume of fresh dissolution medium. Standard stock solution of Loratadine was prepared by adding 40 mg of Loratadine into a 200 ml volumetric flask followed by 20 ml of methanol which was sonicated for about 10 min. 140 ml of diluent was then added, sonicated to dissolve and diluted up to the mark with diluent. About 5.0 ml of standard stock solution was diluted to 100 ml with dissolution medium and filter through 0.45 µ filter to get a standard solution. The absorbance of standard solution and sample preparation were measured at 280 nm using dissolution medium as blank , by comparing with the standard calibration curve.

4.2.2.6. STABILITY STUDIES

Selected Loratadine chewable tablets were further subjected to accelerated stability studies up to three months at 40^0C/ 75% RH..The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors, such as temperature, humidity, and light and to establish a retest period for the drug substance or a shelf life for the drug product and recommended storage conditions (ICH guideline 1996).

4.2.3. FORMULATION DEVELOPMENT AND EVALUATION OF LORATADINE AND PHENYLEPHRINE HYDROCHORIDE EXTENDED RELEASE TABLETS

4.2.3.1. Preformulation study

Preformulation involves the application of biopharmaceutical principles to the physicochemical parameters of drug substance are characterized with the goal of

designing optimum drug delivery system. Preformulation studies relates to pharmaceutical and analytical investigation carried out proceedings and supporting formulation development efforts of the dosage forms of the drug substance. Preformulation yields basic knowledge necessary to develop suitable formulation. It gives information needed to define the nature of the drug substance and provide frame work for drug combination with pharmaceutical excipients in the dosage form. Hence, the following preformulation studies were carried out:

I. Test for identification of Loratadine and phenyl ephdrine.

1. Physical Appearance
2. Solubility analysis
3. Loratadine - excipients compatibility study
4. Phenylephrine - excipients compatibility study

4.2.3.2 Physical Appearance

2.0gm of Loratadine powder was taken on a white piece of paper, spreaded the powder and examine visually.

2.0gm of phenylephrine powder was taken on a white piece of paper, spreaded the powder and examine visually.

4.2.3.3 Solubility studies

Loratadine is sparingly soluble in water. It is freely soluble at pH 1.5 to 2. Increase in the pH drastically changes the solubility of the drug. Loratadine is classified as the Class II according to the Biopharmaceutical Classification of Drugs which means sparingly soluble and highly permeable.(M. Zahirul I. KHAN et al., 2004).

Phenylephrine solubility test was performed as per standard IP procedure.

4.2.3.4 Drug Excipient compatibility studies

API and excipients were thoroughly mixed in predetermined ratio taken and passed through the sieve no.40. The blend was filled in glass vials and closed with gray rubber stoppers and sealed with aluminium seal and charged in to stress condition at 25ºC/60%RH and 40ºC/75%RH. Similarly API was also kept at all conditions as per the sample the samples were observed for any physical change in 1 month duration.

4.2.3.5 Standard curve for Loratadine using 0.1N HCl

Accurately weighed 10 mg of Loratadine and it was dissolved in 0.1N HCl make up the volume with 0.01N HCl in a 100 ml volumetric flask, to give a solution of 100 µg/ml concentration of this served as first standard stock solution. From this stock solution 0.5 ml, 1.0 ml, 1.5 ml, 2.0 ml , 2.5 ml and 3.0ml was taken and diluted to 10 ml using 0.1N HCl to get a solution of 5 , 1 0 , 15, 2 0 , 2 5 and 3 0 µg/ml concentrations. The absorbance of this solution was measured against reagent blank at 283 nm using Shimadzu (UV-1601) spectrophotometer. Standard curve was plotted with concentration on x-axis absorbance on y-axis.

4.2.3.6. Standard curve for Phenylephrine HCl in 0.1N HCl

Accurately weighed 10 mg of Phenylephrine HCl and it was dissolved in 0.1N HCl make up the volume with 0.1N HCl in a 100 ml volumetric flask, to give a solution of 100 µg/ml concentration of this served as first standard stock solution. From this stock solution 0.5 ml, 1.0 ml, 1.5 ml, 2.0 ml , 2.5 ml and 3.0ml was taken and diluted to 10 ml using 0.1N HCl to get a solution of 5 , 1 0 , 15, 2 0 , 2 5 and 3 0 µg/ml concentrations. The absorbance of this

solution was measured against reagent blank at 214 nm using Shimadzu (UV-1601) spectrophotometer. Standard curve was plotted with concentration on x-axis absorbance on y-axis.

4.2.4.1. PREPARATION OF IMMEDIATE RELEASE LAYER OF LORATADINE

All the ingredients were weighed according to the formula. The Loratadine, lactose, Avicel Ph 102, and PG Starch were passed through sieve#30 and blended in an octagonal blender for 20 minutes, then magnesium stearate was passed through sieve #60 and lubrication was done for the blend for five minutes and this preparation is shown in Table 4.12.

Table 4.12: Loratadine immediate release layer

Ingredients (mg/tab)	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6
Loratadine	10	10	10	10	10	10
Lactose DCL 21	99	85	80	90	95	90
Avicel Ph102	76	90	95	87	80	85
Pregelatinized Starch	12	12	12	10	12	12
Magnesium stearate	3	3	3	3	3	3
Total weight	200.0	200	200	200	200	200

4.2.4.2 EVALUATION OF IMMEDIATE RELEASE LAYER OF LORATADINE BLEND

4.2.4.2.1. Bulk density

Bulk density of a compound varies substantially with the method of crystallization, milling or formulation. It is of great importance when one considers the size of a high – dose capsule product or the homogeneity of a low dose formulation in which there are large differences in drug and excipient densities. In addition to bulk density, it is frequently desirable to know the true density of a powder for computation of void volume or porosity of packed powder beds.

An accurately weighed quantity of the granules/ powder (W) was carefully poured into the graduated cylinder and volume (V_0) was measured. Then the graduated cylinder was closed with lid and set into the tap density tester (USP). The density apparatus was set for 500 taps after 750 taps and the volume (V_f) was measured and continued operation till the two consecutive readings were equal. The bulk density and the tapped density were calculated using the following formulae.

Bulk density = Weight of powder(g) / Bulk volume(ml)

4.2.4.2.2. Tapped density

Tapped densities the drug was determined by pouring gently 25 gm of sample through a glass funnel into a 100 mL graduated cylinder. The cylinder was tapped from height of 2 inches until a constant volume was obtained. In USP TAP DENSITY TESTER, Tap density is measured in 500taps, 750 taps & 1250taps with drop/time-299-302.

The tapped density was measured for 500 tapping‘s and 750 tapping‘s giving densities (V_a), and (V_b) with a drop time of 299 to 302 tapping‘s per minute.

If the percentage difference between the _V_a_ and _V_b‘ exceed about 2% than _V_c‘ is measured by 1250 tapping‘s. Either _V_b‘ or _V_c‘ is taken as the final tapped density. The volume occupied by the sample after tapping‘s were recorded and the tapped density was calculated. by the formula below

Tapped density = Weight of powder(g) / Tapped volume(ml)

4.2.4.2.3. Carr’s compressibility index

Compressibility is the ability of powder to decrease in volume under pressure. Compressibility is a measure that is obtained from density determinations. It is also one of the simple methods to evaluate flow property of powder by comparing the bulk density and tapped density. The percentage compressibility of a powder was a direct measure of the potential powder arch or bridge strength and stability.

High density powders tend to possess free flowing properties. A useful empirical guide is given by the Carr‘s index or compressibility index calculated from bulk density and tapped density (Table 4.13). Carr‘s index of each formulation was calculated according to equation given below

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Table 4.13:

Flow properties corresponding to compressibility index as per USP31- NF26

% Compressibility	Flow description
<10	Excellent
11-15	Good
16-20	Fair
21-25	Passable
26-31	Poor
32-37	Very poor
>38	Extremely poor

4.2.4.2.4. Hausner's ratio

Hausner's ratio provides an indication of the degree of densification which could result from vibration of the feed hopper. A lower value of indicates better flow and vice versa. Hausner's Ratio indicates the flow properties of the powder and is measured by the ratio of tapped density to bulk density. It is the ratio of tapped density and bulk density. Hausner found that this ratio was related to inter particle friction and, as such, could be used to predict powder flow properties. Generally a value less than 1.25 indicates good flow properties, which is equivalent to 20% of Carr's index (Table 4.14).

Hausner's Ratio = Tapped density /Bulk density

Table 4.14: Specifications of Hausner's ratio

HAUSNER'S RATIO	TYPE OF FLOW
Less than 1.25	Good Flow (20% Carr's index)
1.25 – 1.5	Moderate (33% Carr's index) (adding glidant normally improves flow)
Greater than 1.5	Poor Flow (Glidant has marginal effect)

4.2.4.2.5. Particle size distribution

Size, shape & surface morphology of drug particles affects the flow, formulation homogeneity, dissolution & chemical reactivity of drugs Particle size of drugs may affect formulation and product efficacy. Certain physical and chemical properties of drug substances are affected by the particle size distribution including: drug dissolution rate, bioavailability, content uniformity, taste, texture, color, stability, flow characteristics, and sedimentation rates. Particle size also has effect on the drug‘s absorption. Satisfactory content uniformity in solid dosage forms depends to a large degree on particle size and the equal distribution of the active ingredient throughout the formulation.

Particle size distribution was carried out in ―Electromagnetic Sieve Shaker‖ (Electrolab EMS-8)

4.2.4.3. PREPARATION OF PHENYLEPHRINE HCl SUSTAINED RELEASE LAYER

Phenylephrine HCl Sustained Release Layer was prepared by wet granulation method according to the formula given in the table no: 4.15. all the Intragranular ingredients were passed through sieve#30 separately, weighed and mixed in geometrical order. Then HPMC K15 was dispersed in require amount of purified water along with iron oxide red and wet granulation was done. The granules obtained were dried until the require LOD was reached. Then the granules were passed through sieve #20 and prelubricated with aerosil which was passed through sieve#40 for 10mins in the blender which was blended with magnesium stearate passed through sieve#60 for 5 mins (Table 4.15)

- Then the tablets were compressed using pillow shaped punches on 8 station bilayer tablet compression machine.

Table 4.15: Phenylephrine HCl sustained release layer

Ingredients (mg/tab)	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6
Intragranular						
Phenylephrine HCl	30	30	30	30	30	30
Avicel Ph 101	148.60	152.60	157.60	153.60	158.60	163.60
Dicalcium Phosphate	65.0	68.0	66.0	70.0	70.0	65.0
HPMC K15M	15.0	15.0	12.0	12.0	15.0	22.0
Natrosol	15.0	15.0	15.0	15.0	10.0	-
Binder Solution						
HPMC K15M	15.0	8.0	8.0	8.0		
Natrosol 250	-	-	-	-	5.0	8.0
Iron oxide red	0.4	0.4	0.4	0.4	0.4	0.4
Purified Water	q.s	q.s	q.s	q.s	q.s	q.s
Prelubrication						
Aerosil	2.0	2.0	2.0	2.0	2.0	2.0
Lubrication						
Stearic acid	9.0	9.0	9.0	9.0	9.0	9.0
Total Weight	300.0	300.0	300.0	300.0	300.0	300.0
Coating						
Opadry clear YS-IR-7006	10.0	10.0	10.0	10.0	10.0	10.0
Purified water	q.s	q.s	q.s	q.s	q.s	q.s

4.2.4.4. EVALUATION OF PHENYLEPHRINE HCl SUSTAINED RELEASE BLEND

4.2.4.4.1. Bulk density

Bulk density of a compound varies substantially with the method of crystallization, milling or formulation. It is of great importance when one considers the size of a high – dose capsule product or the homogeneity of a low dose formulation in which there are large differences in drug and excipient densities. In addition to bulk density, it is frequently desirable to know the true density of a powder for computation of void volume or porosity of packed powder beds.

An accurately weighed quantity of the granules/ powder (W) was carefully poured into the graduated cylinder and volume (V_0) was measured. Then the graduated cylinder was closed with lid and set into the tap density tester (USP). The density apparatus was set for 500 taps after 750 taps and the volume (V_f) was measured and continued operation till the two consecutive readings were equal. The bulk density and the tapped density were calculated using the following formulae.

Bulk density = Weight of powder(g) / Bulk volume(ml)

4.2.4.4.2. Tapped density

Tapped densities the drug was determined by pouring gently 25 gm of sample through a glass funnel into a 100 mL graduated cylinder. The cylinder was tapped from height of 2 inches until a constant volume was obtained. In USP TAP

DENSITY TESTER, Tap density is measured in 500taps, 750 taps & 1250taps with drop/time-299-302.

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If the percentage difference between the _V_a_ and _V_b‘ exceed about 2% than _V_c‘ is measured by 1250 tapping‘s. Either _V_b‘ or _V_c‘ is taken as the final tapped density. The volume occupied by the sample after tapping‘s were recorded and the tapped density was calculated.by the formula below

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4.2.4.4.3. Carr’s compressibility index

Compressibility is the ability of powder to decrease in volume under pressure. Compressibility is a measure that is obtained from density determinations. It is also one of the simple methods to evaluate flow property of powder by comparing the bulk density and tapped density. The percentage compressibility of a powder was a direct measure of the potential powder arch or bridge strength and stability. High density powders tend to possess free flowing properties. A useful empirical guide is given by the Carr‘s index or compressibility index calculated from bulk density and tapped density (Table 4.16). Carr‘s index of each formulation was calculated according to equation given below

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Table 4.16: Flow properties corresponding to compressibility index as per USP31- NF26

% Compressibility	Flow description
<10	Excellent
11-15	Good
16-20	Fair
21-25	Passable
26-31	Poor
32-37	Very poor
>38	Extremely poor

4.2.4.4.4. Hausner's ratio

Hausner's ratio provides an indication of the degree of densification which could result from vibration of the feed hopper. A lower value of indicates better flow and vice versa. Hausner's Ratio indicates the flow properties of the powder and is measured by the ratio of tapped density to bulk density. It is the ratio of tapped density and bulk density. Hausner found that this ratio was related to interparticle friction and, as such, could be used to predict powder flow properties. Generally a value less than 1.25 indicates good flow properties, which is equivalent to 20% of Carr's index (Table 4.17).

Hausner's Ratio = Tapped density /Bulk density

Table 4.17: Specifications of Hausner's ratio

HAUSNER'S RATIO	TYPE OF FLOW
Less than 1.25	Good Flow (20% Carr's index)
1.25 – 1.5	Moderate (33% Carr's index) (adding glidant normally improves flow)
Greater than 1.5	Poor Flow (Glidant has marginal effect)

4.2.4.4.5. Particle size distribution

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Particle size distribution was carried out in ‒Electromagnetic Sieve Shaker‖ (Electrolab EMS-8)

4.2.4.5. EVALUATION OF BILAYER TABLETS (Gandhi PP *et al*., 2010**)**

All the batches of tablets were evaluated for various physical parameters like thickness, weight variation, friability, hardness, drug content and dissolution as per pharmacopoeial standards.

4.2.4.5.1. Thickness (United State Pharmacopoeia-30, 2007**)**

Thickness of tablet is important for uniformity of tablet size. Thickness of tablets can vary with no change in weight because of the difference in the density of the granulation and the pressure applied to the tablets, as well as the speed of the compression machine. Ten tablets were randomly selected and thickness was measured using vernier calipers and recorded.

4.2.4.5.2. Crushing strength (United State Pharmacopoeia-30, 2007**)**

Tablet requires a certain amount of strength or hardness and resistance to friability to withstand mechanical shakes of handling in manufacture, packaging and shipping. Hardness generally measures the tablet crushing strength. Changes in hardness result in differences in disintegration and dissolution characteristics. The crushing strength of the tablet was determined using Schleuniger hardness tester.

4.2.4.5.3. Friability test (United State Pharmacopoeia-30, 2007)

Friability of tablets was determined using Roche Friabilator (Electrolab, Mumbai).The tablets were subjected to the combined effect of abrasions and shock in a Friabilator at 25 rpm and dropping the tablets at a height of six inches in each revolution. Pre weighed sample of tablets was placed in a Friabilator and subjected to 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. The friability is given by the formula:

$F= (1-W_o/W) X 100$

Where, W_o is the weight of the tablets before the test and W is the weight of the tablet after the test.

%Friability = (Loss in weight / Initial weight) x 100

4.2.4.6 *IN VITRO* DRUG RELEASE STUDY

In vitro dissolution of the formulated bilayer tablets was studied using USP Type II Apparatus (Electrolab), employing a paddle stirrer at 50rpm using 900mL of 0.1N HCl at 37±0.5°c as dissolution media. Aliquots of dissolution medium (10mL) were withdrawn at specific intervals of time and analysed for drug content by measuring absorbance at 283nm for Loratadine and at 214 for phenylephrine HCl. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. Cumulative percentage drug released was calculated and plotted against time. In vitro drug release studies were performed for all the trials (in 0.1N HCl as dissolution medium), short term stability studies (at 40ºC/75%RH) for month. Among all the formulations Trial 6 emerged as the overall best formulation found to be promising.

4.2.4.7. STABILITY STUDIES

Selected Loratadine and phenylephrine bilayer tablets were further subjected to accelerated stability studies up to three months at 40^0C/ 75% RH..The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors, such as temperature, humidity, and light and to establish a retest period for the drug substance or a shelf life for the drug product and recommended storage conditions (ICH guideline 1996).