Description

Domperidone is a specific blocker of dopamine receptors. It speeds gastrointestinal peristalsis, causes prolactin release, and is used as antiemetic and tool in the study of dopaminergic mechanisms.

IUPAC name

5-chloro-1-{1-[3-{2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl}propyl]piperidin-4-yl}-2,3 dihydro-1H-1,3-benzodiazol-2-one.

Structural formula

Mechanism of action

Domperidone act as a gastrointestinal emptying (delayed) adjunct and peristaltic stimulant. The antiemetic properties of domperidone are related to its dopamine receptor blocking activity at both the chemoreceptor trigger zone and at the gastric level. It has strong affinities for the D2 and D3 dopamine receptors, which are found in the chemoreceptor trigger zone, located just outside the blood brain barrier, which - among others - regulates nausea and vomiting.

Pharmacokinetic parameters

- Bioavailability: 15%
- Protein binding: 91-93%
- Peak plasma concentration: Within 1 hour
- Metabolism: First pass
- Half-life: 7 Hours

**Drug interactions**

Domperidone decrease absorption of digoxin while increase absorption of aspirin, paracetamol, and oral diazepam. With anticholinergic drugs effect of domperidone antagonized. When administered with promethazine, increased CNS depression.

**Dosing**

The dose of Domperidone is 10-20 mg every 4-8 hours, before meal and breakfast.

**Uses**

- For the management of nausea, vomiting, dyspepsia, heart burn and epigasrtic pain.
- Used for prokinetic action in disorders of gastrointestinal motility.

**Adverse effect**

The main side effects are Galactorrhoea in females and gynaecomastia in male due to production of prolactin.
Description

Ondansetron HCl is a competitive serotonin type 3 receptor antagonist. It is effective in the treatment of nausea and vomiting caused by cytotoxic chemotherapy drugs, including cisplatin, and has reported anxiolytic and neuroleptic properties.

IUPAC name

9-methyl-3-[(2-methyl-1H-imidazol-1-yl) methyl]-2,3,4,9-tetrahydro-1H-carbazol-4-one.

Structural formula

![Structural formula of Ondansetron HCl]

Mechanism of action

Ondansetron is a selective serotonin 5-HT₃ receptor antagonist. The antiemetic activity of the drug is brought about through the inhibition of 5-HT₃ receptors present both centrally (medullary chemoreceptor zone) and peripherally (GI tract). This inhibition of 5-HT₃ receptors in turn inhibits the visceral afferent stimulation of the vomiting center, likely indirectly at the level of the area postrema, as well as through direct inhibition of serotonin activity within the area postrema and the chemoreceptor trigger zone.

Pharmacokinetic parameters

- Bioavailability: 48-70%
Protein binding: 70-76%

Peak plasma concentration: 2 – 4 hours

Metabolism: First pass

Half-life: 5.7 Hours

**Drug interactions**

Domperidone decrease absorption of digoxin while increase absorption of aspirin, paracetamol, and oral diazepam. With anticholinergic drugs effect of Domperidone antagonized. When administered with promethazine, increased CNS depression.

**Dosing**

PO (moderately emetogenic cancer chemotherapy) 8 mg twice daily, administering the first dose 30 min prior to starting emetogenic chemotherapy and the second dose 8 h after the first dose; subsequent 8 mg doses may be given every 12 h for 1 to 2 days after completion of chemotherapy.

**Uses**

Prevention of nausea and vomiting associated with radiotherapy in patients receiving either total body irradiation, single high-dose fraction to the abdomen, or daily fractions to the abdomen; prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin 50 mg/m² or more.

**Adverse effect**

Bradycardia (6%); hypotension (5%); chest pain; Headache (27%); drowsiness/sedation (20%); malaise/fatigue (13%); dizziness (7%); anxiety/agitation (6%); Pruritis (5%); rash (1%); Constipation (9%); diarrhea (7%); dry mouth, abdominal pain.
ANEXURE-III PROFILE OF KEY EXCIPIENTS

INTRODUCTION TO PEG 6000

Nonproprietary names

Macrogols B.P.

Synonyms

Carbowax; Carbowax Sentry, Lipoxol, PEG, Macrogola

Chemical name CAS registry number

α-Hydro-ω-hydroxypropoxy(oxy-1,2-ethanediyl) [25322-68-3]

Description

It is White or off-white in color, and range in consistency from pastes to waxy flakes. It have a faint, sweet odor.

Pharmacopoeial specification

Table I shows the pharmacopoeial specifications USP32-NF27.

Table-I Pharmacopoeial specifications USP32-NF27

<table>
<thead>
<tr>
<th>Test</th>
<th>Specifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viscosity</td>
<td>580 nm²/s</td>
</tr>
<tr>
<td>Density</td>
<td>1.15-1.21 g/cm³</td>
</tr>
<tr>
<td>Hygroscopicity</td>
<td>Not hygroscopic</td>
</tr>
</tbody>
</table>

Solubility

It is Soluble in water and miscible in all proportion with other polyethylene glycols. It is also soluble in acetone, dichloromethane, ethanol (95%), and methanol; slightly soluble in aliphatic hydrocarbon and ether.

Stability and storage

PEG 6000 is chemically stable in air and in solution and do not support microbial growth. It should be stored in well-closed containers in a cool, dry place.
Incompatibilities

The chemical reactivity of polyethylene glycols is mainly confined to the two terminal hydroxyl groups, which can be either esterified or etherified. The antibacterial activity of certain antibiotics is reduced in polyethylene glycol bases, particularly that of penicillin and bacitracin. The preservative efficacy of the parabens may also be impaired owing to binding with polyethylene glycols.

Safety

Polyethylene glycols are widely used in a variety of pharmaceutical formulations. Generally, they are regarded as nontoxic and non-irritant materials.

Regulatory status

PEG 6000 is included in the FDA Inactive Ingredients Database (dental preparations; IM and IV injections; ophthalmic preparations; oral capsules, solutions, syrups, and tablets; rectal, topical, and vaginal preparations). It is included in non-parenteral medicines licensed in the UK. It is included in the Canadian List of Acceptable Non-medicinal Ingredients.
Non-proprietary names

Ammonio Methacrylate Copolymer BP, Amino Methacrylate Copolymer USP-NF

Synonyms

Eastacryl, Eudragit; Kollicoat, MAE

Chemical name CAS registry number

Poly(butyl methacrylate, (2-dimethylaminoethyl) methacrylate, methyl methacrylate) [24938-16-7]

Description

It is white powder with a characteristic amine-like odour.

Pharmacopoeial specification

Table-II shows the pharmacopoeial specifications USP32-NF27.

<table>
<thead>
<tr>
<th>Test</th>
<th>Specifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Particle size</td>
<td>&lt;50 μm</td>
</tr>
<tr>
<td>Loss on drying</td>
<td>2.0%</td>
</tr>
<tr>
<td>Microbial contamination</td>
<td></td>
</tr>
<tr>
<td>Aerobic</td>
<td>10³ CFU/g</td>
</tr>
<tr>
<td>Combined yeast and mould count</td>
<td>10² CFU/g</td>
</tr>
<tr>
<td>Viscosity</td>
<td>3 - 6 mPa·s</td>
</tr>
</tbody>
</table>

Solubility

It is soluble in gastric fluid to pH 5. One g of EUDRAGIT® E 100 or EUDRAGIT® E PO dissolves in 7 g methanol, ethanol, isopropyl alcohol, acetone, ethyl acetate, methylene chloride or 1 N hydrochloric acid to give clear to slightly cloudy solutions.
Stability and storage

EUDRAGIT® E PO Store at temperatures up to 25°C. Protect from moisture. Any storage between 8°C and 25°C fulfils this requirement. Temperatures above 25°C will cause caking of EUDRAGIT® E PO.

Incompatibilities

Generally compatible than compare to aqueous dispersions

Safety

EUDRAGIT® E PO is generally regarded as an essentially nontoxic and non-irritant material.

Regulatory status

EUDRAGIT® E PO is Included in the FDA Inactive Ingredients Database (oral capsules, granules, sublingual tablets, and tablets), nonparenteral medicines licensed in the UK, and in the Canadian List of Acceptable Non-medicinal Ingredients.
Non-proprietary names
Crosscarmellose sodium

Synonyms
Ac-Di-Sol; carmellosum natricum conexum; crosslinked carboxymethylcellulose sodium; Explocel; modified cellulose gum; Nymcel ZSX; Pharmacel XL; Primellose; Solutab; Vivasol.

Chemical name CAS registry number
Cellulose, carboxymethyl ether, sodium salt, crosslinked [74811-65-7].

Description
Crosscarmellose sodium occurs as an odorless, white or grayish white powder.

Pharmacopoeial specification
Table-III shows the pharmacopoeial specifications USP32-NF27

<table>
<thead>
<tr>
<th>Test</th>
<th>Specifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH (1% w/v dispersion)</td>
<td>5.0-7.0</td>
</tr>
<tr>
<td>Loss on drying</td>
<td>≤10%</td>
</tr>
<tr>
<td>Microbial contamination</td>
<td></td>
</tr>
<tr>
<td>Aerobic</td>
<td>10³ cfu/g</td>
</tr>
<tr>
<td>Fungi</td>
<td>10² cfu/g</td>
</tr>
<tr>
<td>Content of water soluble materials</td>
<td>≤10%</td>
</tr>
</tbody>
</table>

Solubility
Crosscarmellose sodium is insoluble in water, although it rapidly swells to 4–8 times its original volume on contact with water. It is practically insoluble in acetone, ethanol and toluene.
Stability and storage

Crosscarmellose sodium is a stable though hygroscopic material, and should be stored in a well closed container in a cool, dry place.

Incompatibilities

The efficiency of Cross carmellose sodium may be slightly reduced by either the wet granulation or direct compression process that contains hygroscopic excipients such as sorbitol. It is not compatible with strong acids or with soluble salts of iron and some other materials such as aluminium, mercury and zinc.

Safety

Cross carmellose sodium is generally regarded as an essentially nontoxic and non-irritant material.

Regulatory status

Cross carmellose sodium is included in the FDA Inactive Ingredients Database (oral capsules, granules, sublingual tablets, and tablets), nonparenteral medicines licensed in the UK, and in the Canadian List of Acceptable Non-medicinal Ingredients.
Non-proprietary names

Crospovidone

Synonyms

Crosslinked povidone; Kollidon CL; Polyplasdone XL.

Chemical name CAS registry number

1-Ethenyl-2-pyrrolidinone homopolymer [9003-39-8]

Description

Crospovidone occurs as an odorless, white powder. Density is 1.22 g/cm³ and it is insoluble in water and most common organic solvents.

Solubility

Crospovidone is practically insoluble in water and most common organic solvents.

Stability and storage

Tablets prepared with crospovidone have good storage properties. Crospovidone is stable and it should be stored in a well-closed container in order to protect it from wide variations of humidity and temperature, which may cause caking. The physical properties of crospovidone remain unchanged for up to 3–5 years if it is stored at moderate temperatures and humidity.

Incompatibilities

Crospovidone is compatible with most organic and inorganic pharmaceutical ingredients. When exposed to a high water level, crospovidone may form molecular adducts with some materials.

Safety

Crospovidone is used in oral pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant material.
Regulatory status

Crosopovidone is included in the FDA Inactive Ingredients Database (IM injections, oral capsules and tablets; topical, transdermal, and vaginal preparations). It is included in nonparenteral medicines licensed in the UK. It is included in the Canadian List of Acceptable Non-medicinal Ingredients.
Nonproprietary names

Sodium starch glycolate

Synonyms

Carboxymethyl starch, sodium salt; Explosol; Glycolys.

Chemical name CAS registry number

Sodium carboxymethyl starch [9063-38-1]

Description

Sodium starch glycolate is a white to off-white, odorless, tasteless, free-flowing granular powder. The PhEur 2005 states that it consists of oval or spherical granules, 30–100 μm in diameter, with some less-spherical granules ranging from 10–35 μm in diameter. Bulk density is 0.756 g/cm³ and it is sparingly soluble in ethanol; practically insoluble in water.

Solubility

Sodium starch glycolate is practically insoluble in methylene chloride. It gives a translucent suspension in water.

Stability and storage

Sodium starch glycolate is hygroscopic; it should be stored in an airtight container in a cool and dry place.

Incompatibilities

Sodium starch glycolate is incompatible with ascorbic acid.

Safety

Sodium starch glycolate is generally regarded as an essentially nontoxic and non-irritant material.

Regulatory status

Sodium starch glycolate is Included in the FDA Inactive Ingredients Database (oral capsules, granules, sublingual tablets, and tablets), non-parenteral medicines licensed in the UK, and in the Canadian List of Acceptable Non-medicinal Ingredients.
LIST OF PUBLICATION


LIST OF POSTERS PRESENTED AT CONFERENCES

- Bhatt Shailendra, Trivedi Priti. Effect of fast dissolving tablets on conditioned placed aversion of Swiss albino mice against marketed formulations. Poster presented at national conference on use of animals and alternatives in biomedical research with emphasis on drug development, organized by Centre for Advanced Studies, department of zoology, University of Rajasthan, Jaipur in collaboration with the LASAI, ISSRF, CPCSEA and PSI. December 2012.
Institutional Animal Ethics Committee  
Banasthali University  

CERTIFICATE

This is certify that the project title “Formulation and evaluation of fast dissolving tablets of antiemetic drugs,” has been approved by the IAEC.

Prof. Vinay Sharma  
Name of Chairman/Member Secretary IAEC:

Dr. Ashok Kumar Agarwal  
Name of CPCSEA nominee:

Signature with date

Chairman/Member Secretary of IAEC:

CPCSEA nominee:

(Kindly make sure that minutes of the duly signed by all the participants are maintained by Office)
CERTIFICATE

This is to certify that the project title “Formulation and evaluation of fast dissolving tablet of anti-emetic drugs animal-male wistar rats.” has been approved by IAEC.

Mr. S.K. Das  
Name of the Chairman / Member Secretary IAEC

Dr. Darpeshkumar Gohel  
Name of the CPCSEA nominee

Signature

(Kindly make sure that minutes of the meeting duly signed by all the participants are maintained by office)
Fast Dissolving Tablet: Convenient Dosage Form for Patients

Priti Trivedi and Shailendra Bhatt

1K.B. Institute of Pharmaceutical Education and Research, Gandhi nagar. (Gujarat)
2Sardar Patel College of Pharmacy, Bakrol, Anand. (Gujarat)

ABSTRACT
Fast dissolving tablets (FDTs) have received ever-increasing demand during the last decade, and the field has become a rapidly growing area in the pharmaceutical industry. Upon introduction into the mouth, these tablets dissolve or disintegrate in the mouth in the absence of additional water for easy administration of active pharmaceutical ingredients. The popularity and usefulness of the formulation resulted in development of several FDT technologies. This review describes various formulations and technologies developed to achieve fast dissolution/dispersion of tablets in the oral cavity, along with excipients, evaluation test, marketed formulation, and drugs explored in this field.

KEYWORDS: Disintegrants, Fast dissolving tablets, Superdisintegrants

INTRODUCTION

It has been estimated that by year 2008 more than 60 blockbuster molecules will go off patent and product sale loss would account for nearly $50 billion in next few year. very high cost of developing a new chemical entity and lack of many new molecule coming in to market, so it is very necessary to optimize the full potential of drug molecule at the early stage of its life cycle. this can be accomplished by incorporating drug in to different drug delivery system.

The oral route of administration still continues to be the most preferred route due to its manifold advantages including ease of ingestion, pain avoidance, versatility and most importantly patient compliance. The most popular dosage forms being tablets and capsules, one important drawback of these dosage forms however is the difficulty to swallow.

Many patients have difficulty in swallowing tablets and hard gelatin capsules and consequently do not take medications as prescribed. It is estimated that 50% of the population is affected by this problem, which results in a high incidence of noncompliance and ineffective therapy.

The difficulty in swallowing or Dysphagia is seen to afflict nearly 35 % of the general population. Many elderly persons will have difficulties because of their hand tremors. Swallowing problems are also common in young individuals because of their under developed muscular and nervous systems. Other groups, who may experience problems in swallowing solid dosage forms, are the mentally ill: they are mentally disabled, uncooperative patient and reduced liquid intake plans or nausea. In some cases such as motion sickness, sudden episode of allergic attack or coughing and an unavailability of water, swallowing tablet may become difficult. This disorder is also associated with number of pathological conditions including Stroke, Parkinson's disease, AIDS other neurological disorders including cerebral palsy.

The demand for solid dosage forms that can be dissolved and suspended in water, chewed, or rapidly dissolved in the mouth is particularly strong in the pediatric and geriatric markets, with further application to other patients who prefer the convenience of a readily administered dosage form.
Table 1: Drugs explored for orally disintegrating tablet

<table>
<thead>
<tr>
<th>Category</th>
<th>Drug</th>
<th>Category</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs</td>
<td>Ketoprofen</td>
<td>Anti depressants</td>
<td>Mitoxantrone</td>
</tr>
<tr>
<td></td>
<td>Piroxicam</td>
<td></td>
<td>Fluoxetine</td>
</tr>
<tr>
<td></td>
<td>Paracetamol</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rofecoxib</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nimesulide</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ibuprofen</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tepoxaline (Canine NSAID)</td>
<td>Anti parkinsonism</td>
<td>Selegiline</td>
</tr>
<tr>
<td>Anti ulcer</td>
<td>Tepoxaline (Canine NSAID)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Famotidine</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lansoprazole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti histaminic</td>
<td>Loratadine</td>
<td>Anti migraine</td>
<td>Sumatriptan</td>
</tr>
<tr>
<td></td>
<td>Diphenhydramine</td>
<td></td>
<td>Rizatriptan benzoate</td>
</tr>
<tr>
<td></td>
<td>Meclizine</td>
<td></td>
<td>Zolmitriptan</td>
</tr>
<tr>
<td>Hypnotics and sedatives</td>
<td>Zolpidem</td>
<td>Anti emetics</td>
<td>Ramosetron Hcl</td>
</tr>
<tr>
<td></td>
<td>Clonazepam</td>
<td></td>
<td>Ondansetron</td>
</tr>
<tr>
<td></td>
<td>Atenolol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti psychotics</td>
<td>Olanzapine</td>
<td>Miscellaneous</td>
<td>Baclofen</td>
</tr>
<tr>
<td></td>
<td>Risperidone</td>
<td></td>
<td>Hydrochlorothiazide</td>
</tr>
<tr>
<td></td>
<td>Pirezepine</td>
<td></td>
<td>Ethazamide</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Tramodol HCl</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Propyphenazone</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Spiranolactone</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Phloroglucinol</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sildenafil</td>
</tr>
</tbody>
</table>

Table 2: Super disintegrants employed in orally disintegrating tablet (55, 56)

<table>
<thead>
<tr>
<th>Super disintegrant</th>
<th>Nature</th>
<th>Properties</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crosspovidone</td>
<td>Crosslinked homo polymer of N-vinyl-2-pyrrolidine</td>
<td>Particle size - 100 μm Insoluble in water</td>
<td>Both swelling and wicking</td>
</tr>
<tr>
<td>Cross carmellose sodium</td>
<td>Cross-linked form of sodium CMC</td>
<td>Particle size 200 mesh Insoluble in water</td>
<td>Swelling</td>
</tr>
<tr>
<td>Sodium starch glycolate</td>
<td>Crosslinked low substituted carboxymethyl ether of poly-glucopyranose</td>
<td>Particle size 140 mesh Insoluble in organic solvents, dispenses in cold water and settles in the form of a highly saturated layer</td>
<td>Water uptake followed by rapid and enormous swelling</td>
</tr>
<tr>
<td>Acrylic acid derivatives(55)</td>
<td>Poly(acrylic acid) super porous hydrogel</td>
<td>Particle size 106 μm</td>
<td>Wicking action</td>
</tr>
<tr>
<td>Effervescent mixture</td>
<td>Citric acid, tartaric acid, sodium bicarbonate</td>
<td>Crystalline nature</td>
<td>Effervescence</td>
</tr>
<tr>
<td>Sodium alginate</td>
<td>Sodium salt of alginic acid</td>
<td>Slowly soluble in water, hygroscopic in nature</td>
<td>Swelling</td>
</tr>
<tr>
<td>NS-300(56)</td>
<td>Carboxy methyl cellulose</td>
<td>Particle size 106 μm DT - 20 S</td>
<td>Wicking type</td>
</tr>
<tr>
<td>ECG-505(56)</td>
<td>Calcium salt of CMC</td>
<td>Particle size 106 μm DT - 80 S</td>
<td>Swelling type</td>
</tr>
<tr>
<td>L-HPC(56)</td>
<td>Low hydroxy propyl cellulose</td>
<td>Particle size 106 μm DT - 90 S</td>
<td>Both swelling and wicking</td>
</tr>
</tbody>
</table>

Because of the increase in the average human life span and the decline, with age, in swallowing ability, oral tablet administration to patients is a significant problem and has become the object of public attention. 4, 5

Traditional tablets and capsules administered with an 8-oz. glass of water may be inconvenient or impractical for some patients. However, some patients, particularly pediatric and geriatric patients, have difficulty swallowing or chewing solid dosage forms6. Many pediatric and geriatric patients are unwilling to take these solid preparations due to fear of choking. For example, a very elderly patient may not be able to swallow a daily dose of antidepressant. An eight-year-old with allergies could use a more convenient dosage form than an antihistamine syrup. A schizophrenic patient in the institutional setting can hide a conventional tablet under his or her tongue to avoid their daily dose of an atypical antipsychotic. A middle-aged woman undergoing radiation therapy for breast cancer may be too nauseous to swallow her H2-blocker. Fast-dissolving/disintegrating tablets (FDTs) are a perfect fit for all of these patients6.

The problem can be resolved by the creation of rapidly dispersing or dissolving oral forms, which do not require water to aid swallowing. The dosage forms are placed in the mouth, allowed to disperse or dissolve in the saliva, and then are swallowed in the normal way. Less frequently, they are designed to be absorbed through the buccal and oesophageal mucosa as the saliva passes into the stomach. In the latter case, the bioavailability of a drug from fast-dispersing formulations may be even greater than that observed for standard dosage forms. Furthermore, side effects may be reduced if they are caused by first pass metabolites. 7, 8

ADVANTAGES: 3, 10

Ease of administration to the patient who can not swallow like mentally ill, disabled, and uncooperative, strock victim, health care facility and bedridden patients. It allows ease of termination of therapy.
It produced rapid on set of action and pregastric absorption increase the bioavailability. pregastric absorption may also reduce the dose of drug if a significant amount of drug is lost through hepatic metabolism. as a result of reduced dosages, it may give improved clinical performance and reduction of unwanted effects.

The highly beneficial feature of this dosage form is the patient who are traveling and busy people who do not have immediate accesses of water can swallow this dosage form very easily.

Fast disintegrating tablet are considered as a new dosages form. Therefore, pharmaceutical companies may get different advantages such as line extension and life cycle management, patent life extension, exclusivity of product promotion and product differentiation.

**FORMULATION PROCESSES IN DEVELOPING FDT:**

**FREEZE-DRYING OR LYOPHILIZATION:** Freeze-drying (lyophilization) is a process in which water is sublimated from the product after freezing. The main advantage being that pharmaceutical substances can be processed at non-elevated temperatures, thereby eliminating adverse thermal effects, and stored in a dry state with relatively few shelf-life stability problems. Freeze-dried forms offer more-rapid dissolution times than other available solid products. The lyophilization process imparts a glassy amorphous structure to the bulking agents and, sometimes, to the drug, thereby enhancing the dissolution characteristics of the formulation.

The resulting tablets are very light and have highly porous structures that allow rapid dissolution. When placed on tongue the unit dissolves almost instantly to release the incorporated drug.

**MOLDING:**

Molding process includes moistening, dissolving, or dispersing the drug with a solvent then molding the moist mixture into tablets (compression molding with lower pressure than conventional tablet compression), evaporating the solvent from drug solution, or suspension at ambient pressure (no vacuum lyophilization), respectively. The molded tablets formed by compression molding are air-dried. As the compression force employed is lower than conventional tablets, the molded tablet results in highly porous structure, which increases the disintegration and dissolution rate of the product. However, to further improve dissolution rate of the product powder mixture should be sieved through very fine screen. As molding process is employed usually with soluble ingredients (saccharides) which offers improved mouth feel and disintegration of tablets. However, molded tablets have low mechanical strength, which results in erosion and breakage during handling.

Takeda (Osaka, Japan) has developed compression molded mixtures, containing an active ingredient, a carbohydrate, barley sufficient amount of water to moisten the surface of particles. After the wetted mass is compressed at low pressure and subsequently dried, porous tablets with sufficient mechanical strength is obtained. The disintegration time is about 30-50 second in mouth.

**COTTON CANDY PROCESS:**

This process is so named as it utilizes a unique spinning mechanism to produce floss-like crystalline structure, which mimic cotton candy. Cotton candy process involves formation of matrix of poly saccharides or saccharides by simultaneous action of flash melting and spinning. The matrix formed is partially recrystallized to have improved flow properties and compressibility. This candy floss matrix is then milled and blended with active ingredients and excipients and subsequently compressed to FDT. This process can accommodate high dosages of drug and offers improved mechanical strength. However, high-process temperature limits the use of this process.

**SPRAY DRYING:**

Highly porous, fine powders are obtained by this method. Allen et al. used this process for preparing FDT. The FDT formulations consisted of hydrolyzed/unhydrolyzed gelatin as supporting agent for matrix, mannitol as bulking agent, and sodium starch glycolate or croscarmellose.
sodium as disintegrating agent. Disintegration and dissolution were further improved by adding effervescent components, i.e. citric acid (an acid) and sodium bicarbonate (an alkali). The formulation was spray dried to yield a porous powder. The FDT made from this method disintegrated in <20 s.  

MASS EXTRUSION:
This technology involves softening the active blend using the solvent mixture of water-soluble polyethylene glycol and methanol and subsequent expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablets.

COMPACTATION:
Using conventional tablet press to make fast dissolving tablet is a very attractive method because of low manufacturing cost and ease of technology transfer. Many strategies have tried to achieve high porosity and adequate tablet strength using tablet press. First, several granulation methods were tried to obtain granules suitable for making FDTs. Wet granulation, dry granulation, etc. methods are used. The second approach is to select special type of excipients as the main component for FDTs. The third approach is to compress tablet at low pressure and apply various after treatment to the soft tablets. The approaches are described in details below.

Several excipients are investigated for rapid disintegration; some of the super disintegrants employed are discussed in Table 2.

Conventional methods:
Wet granulation method:
Bonadeo et al. described a process of producing rapidly disintegrable, mouth-soluble tablets by wet granulation in fluidized bed. Granules with high porosity and low apparent density were obtained, and the tablet made by such granules had rapid disintegration time ranging from 3 to 30 second in the saliva.

Jian et al. developed a rapidly disintegrating tablet for a poorly soluble active ingredient (28). In this method first, nanoparticles were formed. The particles were granulated water soluble or water dispersible excipient using fluid bed; granules were made in to tablet. The tablet had complete dissolution in less than 3 min.

Dry granulation method:
Eoga disclosed a method of making FDTs by dry granulation. Higher density alkali earth metal salt and water soluble carbohydrates do not provide quick disintegration and good mouth feel. Low density alkali metal salts and water soluble carbohydrates are difficult to compress and may cause inadequate content uniformity. So low density alkali earth metal salts or water soluble carbohydrates were pre-compacted, and the resulting granules were compressed in to tablets that could dissolve fast.

Direct compression:
Ishikawa et al. prepared rapidly disintegrating tablet using micro crystalline cellulose (PH-M Series) and low substituted-hydroxypropylecellulose or spherical sugar granules by direct compression method.  

Melt granulation:
Abdelbar et al. prepared FDT by incorporating a hydrophilic waxy binder (super polystate) PEG-6-stearate. Superpolystate is a waxy material with an m.p. of 33-37°C. It not only acts as a binder and increases the physical resistance of tablets, but also helps the disintegration of tablets as it melts in the mouth and solubilizes rapidly leaving no residue. Super polystate was incorporated in the formulation of FDT by melt granulation method where granules are formed by the molten form of this material. Crystallized paracetamol was used as model drug and in addition the formulation included mannitol as a water-soluble excipient and croscarmellose sodium as disintegrating agent.

Phase transition process:
Kuno et al. investigated the disintegration of FDT by phase transition of sugar alcohols using erythritol (m.p.122°C), xylitol (m.p.93-95°C), trehalose (97°C), and mannitol (166°C). Tablets were produced by compressing a powder containing two sugar alcohols with high- and low-melting points and subsequent heating at a temperature between their melting points. Before heating process, the tablets do not have sufficient hardness because of low compatibility. The tablet hardness was increased after heating process, due to the increase of inter particle bonds or the bonding surface area in tablets induced by phase transition of lower melting point sugar alcohol.

Sublimation:
The presence of a highly porous structure in the tablet matrix is the key factor for rapid disintegration of FDT. Even though the conventional tablets contain highly water-soluble ingredients, they often fail to disintegrate rapidly because of low porosity. To improve the porosity, volatile substances such as camphor can be used in tableting process, which sublimated from the formed tablet.

Koizumi et al. developed FDT utilizing camphor, a subliming material that is removed from compressed tablets prepare using a mixture of mannitol and camphor. Camphor was sublimated in vacuum at 80°C for 30 min after preparation of tablets.

Humidity Treatment:
It is known that certain type of sugar change from amorphous state to crystalline state when their solution is spray-dried or used as a binder solution. Further investigations have shown that when an amorphous sugar is treated to go through the humidification and drying process, it change to a crystalline state. This change increase the tablet strength substantially. Liu et al. disclosed a system for making fast dissolving tablets by humidity treatment. In formulating FDTs, one of the important components is the super disintegrants. Several excipients are Investigated for rapid disintegration of FDTs, some of the super disintegrants employed are discussed in Table 2.

PATENTED TECHNOLOGY:
Zydis technology:
The Zydis technology was described in issued to Gregory et al of John Wyeth and Brother, Ltd. and Yanwood et al. of R.P. Scherer. In the Zydis formulation the drug is physically trapped in matrix which is composed of two components. One is a water soluble mixture of saccharides...
(e.g., mannitol) and the other is a polymer (e.g., gelatin). Other carrier polymers commonly used in the Zydis system include partially hydrolyzed gelatin, hydrolyzed dextran, dextrin, alginates, poly (vinyl alcohol), poly-vinylpyrrolidone, acacia, and the mixtures. An especial peetable backing foil was used to package the Zydis unit. Because the water content in the final freeze dried product is to low for microbes grow, the Zydis formulation is also self preserving.\textsuperscript{15}

\textbf{Quicksolve:}\n\begin{itemize}
\item It is a porous solid form also prepared by freeze drying method. In the Quicksolve formulation, the matrix compositions are first dissolve in the first solvent (usually water) and then the solution is frozen. At the temperature when the first solvent remains in the solid form, the frozen solution contacts the second solvent which is substantially miscible with first solvent. The matrix composition should be immiscible to the second solvent. Thus, the first solvent is substantially removed after a few hours of contacting the second solvent to result in a usable matrix.\textsuperscript{15}

Freeze drying is relatively expensive manufacturing process and the final dosages forms are very fragile, lacking physical resistance in standard blister packs. Moreover, this method does not allow accommodating high amount of active drugs. Also, the formulation has poor stability at higher temperature and humidity.\textsuperscript{16}
\end{itemize}

\textbf{Nanocrystal technology:}\textsuperscript{34} This is patented by Elan, King of Prussia. Nanocrystal technology includes lyophilization of colloidal dispersions of drug substance and water-soluble ingredients filled in to blister pockets. This method avoids manufacturing process such as granulation, blending, and tableting, which is more advantageous for highly potent and hazardous drugs. As manufacturing losses are negligible, this process is useful for small quantities of drug.

\textbf{Flash tab technology:}\textsuperscript{25} This is patented by Ethypharm France. This technology includes granulation of excipients by wet or dry granulation method and followed by compressing into tablets. Excipients used in this technology are of two types. Disintegrating agents include reticulated polyvinylpyrrolidone or carboxy methylcellulose. Swelling agents include carboxymethylcellulose, starch, modified starch, microcrystalline cellulose, carboxy methylated starch, etc. These tablets have satisfactory physical resistance. Disintegration time is within 1 min.

\textbf{Orasolv technology:}\textsuperscript{36-37} This technology is patented by CIMA Labs. This includes use of effervescent disintegrating agents compressed with low pressure to produce the FDT. The evolution of carbon dioxide from the tablet produces fizzing sensation, which is a positive organoleptic property. Concentration of effervescent mixture usually employed is 20-25\% of tablet weight. As tablets are prepared at low compression force, they are soft and fragile in nature. This initiated to develop Paksolv,\textsuperscript{40} a special packaging to protect tablets from breaking during storage and transport. Paksolv is a dome-shaped blister package, which prevents vertical movement of tablet with in the depression. Paksolv offers moisture, light, and child resistance packing.

\textbf{Dursolv technology:}\textsuperscript{39} This technology is patented by CIMA Labs. The tablets produced by this technology utilize the conventional tableting equipment. Tablets in this are formulated by using drug, non direct compression fillers, and lubricants. Nondirect compressible fillers are dextrose, mannitol, sorbitol, lactose, and sucrose, which have advantage of quick dissolution and avoid gritty texture, which is generally present in direct compressible sugar. The tablets obtained are strong and can be packed in conventional packing in bottles and blisters. Nondirect compressible fillers generally used in the range of 60-95\%, lubricant in 1-2.5\%.

\textbf{WOW tab technology:}\textsuperscript{40-41} Yamanouchi patented this technology. WOW means with out water. This technology utilizes conventional granulation and tableting methods to produce FDT employing low- and high-moldability saccharides.

Low moldability saccharides are lactose mannitol, glucose, sucrose, and xylitol. High-moldability saccharides are maltose, maltitol, sorbitol, and oligosaccharides. When these low- and high-moldable saccharides used alone tablets obtained do not have desired properties of rapid disintegration and hardness, so combinations are used.

This technology involves granulation of low-moldable saccharides with high-moldable saccharides as a binder and compressing into tablets followed by moisture treatment. Thus tablets obtained showed adequate hardness and rapid disintegration.

\textbf{Dispersible tablet technology:}\textsuperscript{42} Lek, Yugoslavia patents this technology. It offers development of FDT with improved dissolution rate by incorporating 8-10\% of organic acids and disintegrating agents. Disintegrating agent facilitates rapid swelling and good wetting capabilities to the tablets that results in quick disintegration.

Disintegrants include starch, modified starches, microcrystalline cellulose, alginic acid, cross-linked sodium carboxy methyl cellulose and cyclodextrins. Combination of disintegrants improved disintegration of tablets usually less than 1 min.

\textbf{Pharmaburst technology:}\textsuperscript{8} SPI Pharma, New Castle, patents this technology. It utilizes the co processed excipients to develop FDT, which dissolves within 30-40 s. This technology involves dry blending of drug, flavor, and lubricant followed by compression into tablets. Tablets obtained have sufficient strength so they can be packed in blister packs and bottles.

\textbf{Frosa technology:}\textsuperscript{9} Akina patents this technology. It utilizes the concept of formulating plastic granules and compressing at low pressure to produce strong tablets with high porosity. Plastic granules

\begin{itemize}
\item Composed of:
  \begin{itemize}
  \item Porous and plastic material,
  \item Water penetration enhancer, and
  \item Binder.
  \end{itemize}
\end{itemize}

The process involves usually mixing the porous plastic material with water penetration enhancer and followed by granulating with binder. The tablets obtained have excellent hardness and rapid disintegration time ranging from 15 to 30 s depending on size of tablet.
Oraquick:
This technology is patented by K.V Pharmaceuticals.43 It utilizes taste masking micro sphere technology called as micromask, which provides superior mouth feel, significant mechanical strength, and quick disintegration/dissolution of product. This process involves preparation of microparticles in the form of matrix that protects drug, which can be compressed with sufficient mechanical strength. Low heat of production in this process makes it appropriate for heat sensitive formulations. Some FDT not require special packaging, so they can be packed in push through blisters or bottles.

Ziplets/advatab: 44
This technology is patented by Pessano con Bornago, Italy. It utilizes water-insoluble ingredient combined with one or more effective disintegrants to produce FDT with improved mechanical strength and optimal disintegration time at low compression force. This technology handles high drug loading and coated drug particles and does not require special packaging, so they can be packed in push through blisters or bottles.

Flash heat process:
Fuisz has introduced the shearform technology to make FDTs.24 The shearform technique utilizes a unique spinning mechanism to produce floss like crystalline structure, much like cotton candy. In this process the feedstock is subjected to the centrifugal force and to a temperature gradient simultaneously. An internal flow is created by this condition to force the flowing mass out of the opening provided in the perimeter of a spinning head. The mass is cooled down as it comes out of the opening to form a discrete fiber structure, as seen in cotton candy. The speed of spinning is about 3,000–4,000 rpm, and the temperature gradient is about 180–250°C. The carrier material includes the saccharides, poly saccharides, and mixture thereof.

The produced floss needs to be recrystallized to form free flowing granules of self binding properties. There are two system used to create shearform floss, having self binding properties. 25-26

In the first system, mixture of xylitol, a mixture of saccharide-based carrier and one more additional sugar alcohol, preferably with sorbitol, were used to create shearform. This system named as “single floss” or “uni floss”. The second system utilizes two separate flosses, one is xylitol-containing binder flosses and other is base flosses which contain different sugar alcohol or saccharides. The two flosses are combined together, and this system is termed as “dual floss”.

Approach for Taste masking:
For conventional tablet formulation, taste masking is not a critical issue to be addressed, because tablets are supposed to be swallowed quickly with plenty of water. FDTs stay in mouth longer then the conventional tablets. Some FDTs take up to more then one minute in mouth. Taste masking is must for bitter drugs.

To overcome this problem various approaches are studied.40 Incorporation of sweeteners and flavors:
To provide pleasant taste and mouth feel Sweeteners and flavors are used in many FDT formulations.

In OraSolve formulation a effervescence couple was added to provide a tingling effect as carbon dioxide is generated during disintegration, as these tablets compressed at low pressure, the coating on the drug particle remain intact during compression. This contributes to better taste masking.

Phase separation approach for taste-masked microcapsules.57

Micro caps process used micro encapsulation technology.

• Extrusion method.
• Flash tab technology.
• Blending with cyclodextrin 58

Coating crystals, granules and pellets with aqueous dispersions of methacrylic acid polymers.

Determination of disintegration time of FDTS:
FDTs should be strong enough to survive rough handling during manufacturing and shipping process, and yet friable enough to instantly dissolve or disintegrate into small particles to quickly release their active ingredients in patient mouth. Conventional disintegration taste for ordinary tablets may not allow precise measurement of the disintegration time of FDTs.

Generally, the method described in U.S. Pharmacopoeia can produce data for evaluation of the disintegration time. It is also possible to evaluate the tendency of disintegration kinetics by visual examination. However these examinations are not sufficiently objective. 59

In order to predict the disintegration time of FDTs and effects of different formulation parameters, a few method have been proposed.59,62

In vivo Determination of Disintegration time:
It can be conducted on volunteers. Volunteers are usually randomized to receive the treatment and then directed to clean their mouth with water. 62 Tablets are placed on their tongues, and then time for disintegration is measured by immediately starting a stopwatch. The volunteers are allowed to move FDTs against the upper roof of the mouth with their tongue and to cause a gentle tumbaling action on the tablet without biting on it or tumbaling it from side to side. Immediately after the last noticeable granule has disintegrated, the stopwatch is stopped and the time recorded.
In vitro determination of disintegration time:

**Modified U.S. Pharmacopoeia Method:**
Instead of using the disintegration apparatus described in the U.S. Pharmacopoeia, a modified method has been proposed. The disintegration apparatus was same as the USP dissolution test apparatus 2, which uses a paddle stirring element.

And 1000 ml cylinder vessel at 37°C. Distilled water was chosen for disintegration medium, instead of buffer solution. A tablet to be tasted put on the bottom of the sinker, which was placed on the middle of the vessel and hung by a hook to the lid of the vessel with a distance of 6 to 8.5 cm. Disintegration time was determined at the point at which the tablet disintegrated and passed through the screen of sinker completely. The opening of mesh of sinker was 3-3.5 mm in height and 3.5-4 mm in width.

**Method Using Texture Analyzer:**
A Texture Analyzer (Stable Micro System, U.K.) was applied to measure the beginning and ending time of disintegration. A tablet was adhered to the bottom of a probe, which was attached to the load cell, with a very thin layer of glue or double-sided Scotch tape. The tablet under a constant force was immersed in a definite volume of distilled water. The time for the tablet to disintegrate was determined by measuring the distance the probe traveled into the tablet. Typical time distance profiles generated by the Texture Analyzer software enabled the calculation of beginning and ending of disintegration time.

**Method Using a CCD Camera:**
This CCD camera apparatus is comprised of two distinct sections, a disintegration component and a measurement device. The mode of measurement involves the continuous of pictures by the CCD camera to record the disintegration time course. The acquired picture are simultaneously transferred to the computer and stored. The key point of this apparatus is to combine the detailed picture obtained by the CCD camera.

**Evaluation of FDTs:**
Evaluation parameters are discussed as follow:

**Hardness/crushing strength:**
The limit of crushing strength of FDTs usually kept in lower range to facilitate early disintegration in mouth. The crushing strength of the tablet may be measured using conventional hardness taster.

**Friability:**
To achieve % friability within limit for an FDT is the challenge to the formulator science all methods of manufacturing FDT are responsible for increasing % friability values. Thus it is necessary that this parameter should be evaluated and the results are with in bound limits (0.1-0.9%).

**Wetting time and water absorption ratio:**
Wetting time of a dosages form is related with the contact angle. Lower wetting time give a quicker disintegration of tablet.

The wetting time of a tablet can be measured using a simple procedure. Five circular tissue paper of 10 cm diameter are placed in a Petridish with a 10 cm diameter. Ten milliliter of water soluble dye (eosin) solution is added to pertidish. A tablet is placed on the surface of tissue paper. The time required for the water to reach the upper surface is noted as wetting time.

For measuring water absorption ratio the weight of tablet before keeping in petridish is noted \( W_a \). The wetted tablet from the Petridish is taken and reweigh \( W_b \). The water absorption ratio then can be determined according to the following equation:

\[
R = 100 \left( \frac{W_a - W_b}{W_a} \right)
\]

**Moisture uptake study:**
Ten tablets from each formulation were kept in a desiccator over calcium chloride at 37°C for 24 h. The tablet is then weighed and exposed to 75% relative humidity, at room temperature for 2 weeks. Required humidity was achieved by keeping saturated sodium chloride solution at the bottom of the desiccator for 3 days. One tablet as control (without superdisintegrant) was kept to access the moisture uptake due to the other excipients. Tablets were weighed and % increase in weight was recorded.

**Disintegration Test:**
The time of disintegration for FDT is < 1 min and actual disintegration time that patient can experience ranges from 5 to 30 sec. The standard procedure for performing disintegration test for these dosage forms has several limitations. Various disintegration methods developed are discussed above.

**Dissolution Test:**
Dissolution medium such as 0.1 N HCl and buffers (pH 4.5 and 6.8) should be evaluated for FDT same way as conventional tablets. USP dissolution apparatus 1 and 2 can be used. USP basket 1 apparatus may have some applications, but some times tablet fragments or disintegrated tablet masses may become trapped on the inside top of the basket where little or no effective stirring occurs, yielding irreproducible dissolution profile. Kancke proposed USP 2 paddle apparatus, which is most suitable and common choice for FDTs, with a paddle speed of 50 rpm commonly used. Typically, the dissolution of FDT is very fast when using USP monograph conditions; hence slower paddle speed may be utilized to obtain a profile.

The USP 2 paddle apparatus at 50-100 rpm is suitable for dissolution testing of taste-marked drug as well. The media used for taste-masked drug should match that of the finished product to maximize the value of the test. High-performance liquid chromatography is required to analyze dissolution aliquots due to the presence of UV absorbing components, specially flavors and sweeteners.

**Clinical studies:**
In vivo studies were performed on oral fast-disintegrating dosage forms to investigate their behavior in the oral esophageal tract, their pharmacokinetic and therapeutic efficacy, and acceptability. Zydis’s residence time in the mouth and stomach, and its transit through the esophageal tract, was investigated using gamma-scintigraphy. Its dissolution and buccal clearance was rapid; the esophageal transit time and stomach emptying time were comparable with those of traditional tablets, capsules, or liquid forms. A decreased intersubject variability in transit time also was observed. Zydis also showed good therapeutic efficacy and patient acceptability — particularly...
in children or when easy administration and rapid onset of action were required (such as for patients undergoing surgery).

The fast-disintegrating forms examined showed improved pharmacokinetic characteristics when compared with reference oral solid formulations. For example, the absorption rate of the acetaminophen Flashtab was higher than that of the brand leader, while having the same bioavailability. Increased bioavailability and improved patient compliance were observed in Lyoc formulations for different drugs such as chloroquine, glafenine, spironolactone, and propyphenazone. Using Zydus, all the drugs that can be absorbed through the buccal and esophageal mucosa exhibited increased bioavailability and side-effect reduction. This is helpful particularly in actives with marked first-pass hepatic metabolism. Finally, the suitability of FDTs for long-term therapy also was assessed. Lyoc formulations containing aluminum were positively tested in patients with gastrointestinal symptoms.

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Development and Evaluation of Fast Dissolving Tablets of Ondansetron HCl Using Vacuum-Drying Approach

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Abstract

The aim of present investigation was to design ‘Traveler Friendly Drug Delivery System’ of Ondansetron HCl. Conventional tablet of Ondansetron HCl are not capable of rapid action and water is also needed. Tablets were formulated by direct compression using mannitol, superdisintegrants and camphor, whereby camphor, a subliming material, is removed by sublimation from compressed tablets. Tablets prepared with camphor (20%) and Ac-Di-Sol (6%) exhibited disintegration time (21 s) and friability (0.49%). Further to decrease the disintegration time and friability aerosol (0.5%) is used as lubricant, which gives least disintegration time (19 s) and friability (0.32%).

Keywords: Vacuum-drying technique, camphor, mannitol, fast dissolving tablet, Ac-Di-Sol.

Introduction

The tablet is the most widely used dosages form because of its convenience in terms of self administration, compactness, and ease of manufacturing. However, geriatric and pediatric patients experience difficulty in swallowing conventional tablets, which leads to poor patient’s compliance. We often experience inconvenience in swallowing conventional tablets when water is not available. To overcome this weakness, scientists have developed innovative drug delivery system known as fast dissolving tablets (FDT). This is a novel technology in which the dosages form is placed in the mouth and disintegrate in the oral cavity within 60 s or less without the need of water. The benefits in terms of patient’s compliance, rapid onset of action, increased bioavailability and good suitability makes these tablets popular as a dosages form of choice in the current market (Bi et al., 1996, Change et al. 2000). The basic approach used in the development of the fast dissolving tablet is the use of superdisintegrants. Another approach used in the development of FDT is maximizing pore structure of the tablets. Freeze-drying (Corveleyen et al. 1997). Technique has been tried by researchers to maximize the pore structure of tablet matrix. Freeze-drying method require specific machine for production and packaging and its yield a fragile and hygroscopic material. The compressed tablets prepared with crystalline cellulose and low- substituted hydroxypropylcellulose (L-HPC) rapidly disintegrate in saliva (or a small amount of water) in the mouth of human (Watanabe et al. 1995). However, patients sometimes feel rough texture in their mouth due to incomplete solubilization of this type of tablet in saliva.

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To eliminate the rough texture in the mouth, we attempt to use a water soluble material Mannitol and Ac-Di-Sol instead of crystalline cellulose and L-HPC, in the preparation of this type of tablet. The compressed tablets prepared using mannitol did not rapidly dissolve in saliva since it is difficult for water to penetrate into the tablet due to its low porosity. We therefore investigated a new convenient method of preparing compressed tablets with high porosity, which dissolve rapidly in the mouth, using mannitol and Ac-Di-Sol with a subliming material. We chose camphor as a subliming material since it can be used as a medicinal drug.

Ondansetron HCl is a potent antiemetic drug (Aurora et al. 2005), indicated for the treatment and/or prophylaxis of postoperative or chemotherapy- or radiotherapy-induced emesis and also used in the early onset of alcoholism (Johanson et al. 2000). In general, emesis is preceded with nausea and in such condition it is difficult to administer drug with a glass of water; hence it is beneficial to administer such drugs as FDTs.

Conventional tablets of Ondansetron HCl are incapable of the rapid action required for faster onset of drug effect and immediate relief from nausea and vomiting. Thus, the present study aims to develop FDT of Ondansetron HCl able to rapidly dissolve in saliva and ensure immediate relief from nausea and vomiting, serving dual purpose of increasing patient compliance, particularly for pediatric and geriatric patients, and providing immediate relief.

Material and Methods

Material

Ondansetron HCl was obtained as a gift sample from Cadila Pharmaceutical limited, Ahmedabad. Cross carmellose sodium (Ac-Di-Sol), Crosspovidone, and sodium starch glycolate were received as a gift sample from Torrent Research Center Ahmedabad, Camphor were obtained from a local ayurvedic pharmacy. Mannitol and magnesium stearate were purchased from S.D. Fine Chemicals, Mumbai. All other chemicals used in the study were of analytical reagent grade.

Methods

Selection of camphor concentration for formulation of tablets

Before formulation of tablets, the best concentration of camphor was screened out. Tablets were prepared in various batches containing different concentration of camphor with mannitol (Table 2). Camphor was mixed with mannitol in different concentration, and tablets were compressed. Tablets were subjected to Vacuum-drying using vacuum oven (Erection Engineering Pvt. Ltd., Ahmedabad, India) for 3-4 h at temperature ranging from 50-60 °C and at a pressure of 300 mm Hg. The concentration of camphor screened was used for the final formulation of tablet (Table 1).

Preparation of tablets

Tablets were prepared by direct compression. All the raw materials were passed through # 60 sieves prior to mixing. Ondansetron HCl, and the superdisintegrants (Cross povidone /Ac-Di-Sol / Sodium starch glycolate), camphor (20%), and mannitol (as much as required) were blended. The powder blend was lubricated with magnesium stearate (1%) and aerosil (0.5%). The powder blend was compressed on a 10 station mini press tablet machine (CPMD 3-10, Chamunda Pharma Machinery Pvt. Ltd., Ahmedabad, India.) equipped with 9 mm concave punch. The tablets were dried in a vacuum oven for 4 h at a temperature of 60 °C and at a pressure of 300 mm Hg.
Table 1. Tablet formulations

<table>
<thead>
<tr>
<th>Formulation</th>
<th>S1</th>
<th>S2</th>
<th>S3</th>
<th>S4</th>
<th>S5</th>
<th>S6</th>
<th>S7</th>
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<td>139.5</td>
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<td>135.5</td>
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<td>12</td>
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<td>-</td>
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<tr>
<td>Ac-Di-Sol</td>
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<td>-</td>
<td>8</td>
<td>12</td>
<td>16</td>
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<td>-</td>
<td>1.25</td>
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</tr>
</tbody>
</table>

Evaluation of tablet properties

The hardness of tablets was measured using Pfizer hardness tester. Tablet Friability was measured using Roche Friabilator according to specification given in IP 1996. This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm for 4 min. The tablets were dedusted, and the loss in weight caused by the fracture and abrasion was recorded as the % weight loss. Friability below 1% was considered acceptable.

\[
F\% = \left(1 - \frac{W}{W_0}\right) \times 100
\]

Where, \(W_0\) is initial weight of the tablets before the test and \(W\) is the weight of the tablets after test.

The wetting time of the tablets was measured using a piece of tissue paper folded twice was kept in a culture dish (internal diameter 5.5 cm) containing ~6 mL of purified water. A tablet having a small amount of amaranth powder on the upper surface was placed on the tissue paper. The time required to develop a red color on the upper surface of the tablet was recorded as the wetting time (Kuchekar et al. 2004).

Disintegration of fast dissolving tablets is achieved by saliva in the mouth, however amount of saliva in the mouth is limited and no tablet disintegration test was found in USP and IP to simulate in vivo condition. The disintegration time was measured using a modified disintegration method. According to this method, a Petri dish of 10 cm diameter was filled with 10 ml of distilled water, the tablet was carefully places at the center of the Petri dish, and the time necessary for the complete disintegration of the tablet in to fine particles was noted as disintegration time.

The optimized tablet was also observed by scanning electron microscope (ESEM TMP with EDAX, Philips, Holland). Pictures were taken at an excitation voltage of 30 kv and a magnification of 120 X

In-vitro drug release

Tablet test condition for the dissolution rate studies were used according USP specification using USP 24, type I apparatus. The dissolution medium was 900 ml of Phosphate buffer (pH 6.8). The temperature of the dissolution medium and the rate of agitation were maintained at 37± 0.5°C and 100 rpm respectively. Aliquots of 10 ml of dissolution medium were withdrawn at specific time interval and the volume replaced by fresh dissolution medium, pre warmed to 37± 0.5°C. The drug concentration was determined spectrophotometrically at 249 nm using UV spectrophotometer (Shimadzu S 1700, Japan).
**Stability Study**

Stability study for Representative samples (S4, and S8) were carried out at 25± 2°C/60± 5% RH, and 40± 2°C/75± 5% RH for 6 month. The effect on various tablet properties such as disintegration time, Friability and hardness was measured. A value of P< 0.05 was considered as significant.

**Result and Discussion**

*Selection of camphor concentration for formulation of tablets*

In first experiment weight before and after sublimation of camphor was carried out (Table 3). The decrease in the mean weight corresponded to the weight of camphor added to the tablets. We concluded that almost all camphor had sublimated from the tablets. Based on the agreement between the weight of camphor added and the weight decrease observed. As shown in (Table 2), there were no pre-camphor sublimation difference in hardness among the tablets prepared using various concentration of camphor. The pre-camphor sublimation hardness of tablets prepared using various concentration of camphor was in range of 6.3-6.8 kg/cm². Unfortunately, the hardness of these tablets after sublimation of camphor decreased and consequently tablets with 40% camphor concentration did not remain compressed. However tablets prepared with camphor concentration of less than 30% remain compressed. The tablets prepared using camphor concentration of 20% have sufficient strength for practical use, and rapidly disintegrated in 31 s. Rapidly disintegration of tablets may be related to an improvement in the ability of water to penetrate in to tablet due to high porosity obtained by the increase in the number of pores after sublimation of camphor. The result showed that the disintegration time was significantly affected by the camphor concentration, with the camphor concentration increasing with the decrease in the disintegration time. From the result obtained camphor 20% was screened out for the final formulation of tablets.

<table>
<thead>
<tr>
<th>Conc. of camphor</th>
<th>Hardness (kg/cm²) before sublimation</th>
<th>Hardness (kg/cm²) after sublimation</th>
<th>Disintegration time (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>6.8</td>
<td>-</td>
<td>&gt; 130</td>
</tr>
<tr>
<td>10</td>
<td>6.5</td>
<td>4.2</td>
<td>38±2.01</td>
</tr>
<tr>
<td>20</td>
<td>6.5</td>
<td>3.5</td>
<td>31±3.10</td>
</tr>
<tr>
<td>30</td>
<td>6.4</td>
<td>1.5</td>
<td>8±1.82</td>
</tr>
<tr>
<td>40</td>
<td>6.3</td>
<td>Very fragile</td>
<td>-</td>
</tr>
</tbody>
</table>

*values given as mean ± standard deviation (n=3)

**Table 3. Tablet weight (mg) before and after sublimation**

<table>
<thead>
<tr>
<th>Camphor (mg)</th>
<th>Before sublimation</th>
<th>After sublimation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>198±2.67</td>
<td>198±1.12</td>
</tr>
<tr>
<td>20</td>
<td>201±3.12</td>
<td>181±2.01</td>
</tr>
<tr>
<td>40</td>
<td>203±2.71</td>
<td>180±2.19</td>
</tr>
<tr>
<td>60</td>
<td>198±2.10</td>
<td>138±1.43</td>
</tr>
</tbody>
</table>

*values given as mean ± standard deviation (n=3)
Evaluation of tablet properties

Tablets were evaluated for various physical parameters such as hardness, friability, disintegration time and wetting time (Table 4). Hardness of all batches was found in range of 3.4-3.6 kg/cm². Friability of all batches was less than 1%, which is regarded to be good mechanical resistance. It is worthwhile to note, however, that the addition of camphor also resulted in increased friability, probably due to generation of porous structure in the tablet matrix. So, in order to decrease the tablet’s friability, colloidal silicon dioxide (aerosil) was added in batch S8, because aerosol helps to restore the bonding properties of excipients (Shiyousaku et al. 1999). The addition of aerosol resulted in an appreciable decrease in the percent of friability from 0.49% in batch S4 to 0.32% in batch S8 and a marginal decrease in disintegration time from 21 s in batch S4 to 19 s in batch S8.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Hardness (kg/cm²)</th>
<th>Friability (%)</th>
<th>Disintegration time (s)</th>
<th>Wetting time (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>3.5±0.15</td>
<td>0.50±0.10</td>
<td>27±2.23</td>
<td>24±1.10</td>
</tr>
<tr>
<td>S2</td>
<td>3.4±0.05</td>
<td>0.51±0.21</td>
<td>26±2.10</td>
<td>22±1.13</td>
</tr>
<tr>
<td>S3</td>
<td>3.4±0.73</td>
<td>0.49±0.02</td>
<td>23±1.80</td>
<td>20±1.12</td>
</tr>
<tr>
<td>S4</td>
<td>3.4±0.19</td>
<td>0.49±0.10</td>
<td>21±1.17</td>
<td>18±1.03</td>
</tr>
<tr>
<td>S5</td>
<td>3.4±0.03</td>
<td>0.50±0.19</td>
<td>26±1.91</td>
<td>23±1.31</td>
</tr>
<tr>
<td>S6</td>
<td>3.6±0.09</td>
<td>0.48±0.03</td>
<td>29±2.30</td>
<td>25±1.23</td>
</tr>
<tr>
<td>S7</td>
<td>3.5±0.17</td>
<td>0.47±0.07</td>
<td>28±2.01</td>
<td>23±1.19</td>
</tr>
<tr>
<td>S8</td>
<td>3.5±0.10</td>
<td>0.32±0.11</td>
<td>19±1.25</td>
<td>14±1.03</td>
</tr>
<tr>
<td>S9</td>
<td>3.5±1.13</td>
<td>0.40±0.31</td>
<td>35±1.57</td>
<td>31±1.01</td>
</tr>
</tbody>
</table>

*values given as mean ± standard deviation (n=3)

The disintegration time of the FDT showed wide variation, thus indicating that the type of superdisintegrants and camphor concentration had an effect on disintegration time. In corporation of cross carmellose sodium (Ac-Di-Sol) (6%) with camphor showed quick disintegration time 21s followed by Crosspovidone and sodium starch glycolate, while tablet prepared with Ac-Di-Sol alone disintegrated in 35 s. The porous structure induced in the tablet matrix due to sublimation of camphor was responsible for faster water uptake. Thus, facilitating the swelling action of Ac-Di-Sol and allowing faster disintegration which has been reported in the literature (Koizumi et al. 1997, Shimizu et al. 2003).
Figure 1. SEM micrograph of the cross sectional view of a high porosity fast dissolving tablet after sublimation of camphor.

Figure 1 shows a micrograph of the cross section of a high porosity fast dissolving tablet. It was found that many porous cavities in the tablet were formed due to the sublimation of camphor. The probable reason of delayed disintegration with Crosspovidone and sodium starch glycolate might be due to their tendency to gel more than Ac-Di-Sol. Opposite result was observed at with fraction higher than 6% of Ac-Di-Sol. Ac-Di-Sol is a superdisintegrant of excellent disintegration ability. It swells to a large extent when in contact with water. However, Ac-Di-Sol is made by crosslinking of sodium carboxymethylcellulose which greatly reduce its water solubility, while permeating the material to swell and absorb water in amounts of several times its own mass without losing its fibrous structure. Such hydration makes Ac-Di-Sol more viscous and adhesive, when added in higher concentration (Bi et al. 1999). This can be the possible reason for increasing of wetting and disintegration time of the tablet containing more than 6% of Ac-Di-Sol. Tablet containing sodium starch glycolate with camphor having disintegration time higher than Ac-Di-Sol and Crosspovidone. The ‘superdisintegrant’ action of sodium starch glycolate is governed by extensive swelling, contact of water with sodium starch glycolate leads to the formation of viscous plugs (Augsburger et al. 2001). Due to increase in the viscosity, further uptake of water may be retarded; and the tablets break in to large floccules instead of disintegrating in to smaller particles. This might be the reason for increased disintegration time with increase amount of sodium starch glycolate.

Drug release profiles for different formulations are shown in Figure 2. Tablets prepared with crosspovidone, Ac-Di-Sol and sodium starch glycolate in combination with 20% camphor released about 100% with in (6-7 min), (2-3 min) and (8 min) respectively, while tablets prepared without camphor released 100% drug with in 10 min . The overall release rate of
Ondansetron HCl from the tablets containing 6% Ac-Di-Sol (S4 and S8) with 20% camphor was highest. Erosion of tablets is probably an important mechanism of drug release, since very rapid disintegration was noticed with these tablets by visual inspection during dissolution and disintegrations studies. The tablet containing more than 6% Ac-Di-Sol took more time for complete release of Ondansetron HCl. This might be due to higher viscosity and adhesiveness in cases where Ac-Di-Sol is added in higher fractions. Tablets prepared with sodium starch glycolate showed slower release. These tablets showed rapid ability to hydrate with the formation of a swollen sponge like arrangement, which might create a barrier for drug dissolution.

![Figure 2](image-url). Drug release profile of different formulations

The result of stability testing indicate that there is no significant change in disintegration time, friability and hardness at 25 ± 2°C/60 ± 5% RH, and 40 ± 2°C/75 ± 5% RH was observed.

**Summary**

The results of different formulations revealed that Ac-Di-Sol (6%) was the most effective superdisintegrant among those employed in the study, but the use of superdisintegrants alone was not able to fulfill the requirements of an FDT, and so it was accompanied by a vacuum-drying technique using camphor as a subliming agent. Camphor was able to generate porous structure in the tablet matrix, decreasing the disintegration time below 30 s by acting synergistically with superdisintegrants. Thus it is concluded that by adopting a systemic formulation approach, FDTs of Ondansetron HCl could be formulated using superdisintegrants in combination with a vacuum-drying technique.

**References**


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Taste Masking of Ondansetron Hydrochloride and Formulation of Fast Dissolving Tablets

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ABSTRACT
The purpose of this research was to mask the intensely bitter taste of Ondansetron HCl and to formulate a Fast dissolving tablet (FDT) of the taste-masked drug. Taste masking was done by complexing Ondansetron HCl with aminoalkyl methacrylate copolymer (Eudragit EPO) in different ratios by the extrusion method and Novel wet granulation method. Taste masked complex were analyzed with FTIR, DSC and XRD. Drug-polymer complexes (DPCs) were tested for drug content, in vitro taste in simulated salivary fluid (SSF) of pH 6.8, and molecular property. In vitro release profile obtained at SSF pH 6.8 indicate that perceivable amount of drug will not be released in saliva. The taste masked granules were directly compressed in to tablets using crosscarmellose sodium (Ac-Di-Sol) as a super disintegrantes. Tablets of batch F4 containing microcrystalline cellulose and lactose in the ratio 1:1 and 6% wt/wt Ac-Di-Sol showed faster disintegration, within 34 seconds, than the marketed tablet (102 seconds). Tablets of batch F4 also revealed rapid drug release (t90, 240 seconds) at acidic pH 1.2 of the stomach compared with marketed formulation (t90, 600 seconds). The observed polymer interaction and reduced crystallinity may be reason for increased dissolution rate. Thus, results conclusively demonstrated successful masking of taste and rapid disintegration and dissolution of the formulated tablets.

Key words: Taste masking, Ondansetron HCl, Fast dissolving tablet, Eudragit EPO.

INTRODUCTION
Although various novel and advanced drug delivery systems have been introduced in for therapeutic use, the popularity of oral dosages form, particularly tablets have not been eclipsed, because tablets still have numerous advantages. However, one important drawback of tablets as a dosages form is the need to swallow. Dysphasia or general difficulties in swallowing of the tablets may be a problem for geriatric, pediatric [1] or traveling patients, if the latter do not have
access to water. Among the dosage forms developed to facilitate ease of medication, the fast dissolving tablet (FDT) is one of the most widely employed commercial products [2-4]. The FDT has remarkable disintegration properties; it can rapidly disintegrate without water in the mouth within a few seconds. When an FDT is placed in the oral cavity, saliva quickly penetrates into the pores causing rapid disintegration. More than 50% of the pharmaceutical products are orally administered for several reasons, and undesirable taste is one of the important formulation problems encountered with such oral products. Taste of a pharmaceutical product is an important parameter for governing compliance. Thus, taste masking of oral pharmaceuticals has become an important tool to improve patient compliance and the quality of treatment, especially in pediatrics. Therefore, formulation of taste-masked products is a challenge to the pharmacists [5-6]. Ondansetron HCl is a potent antiemetic drug indicated for the treatment and/or prophylaxis of postoperative or chemotherapy- or radiotherapy-induced emesis, and is also used in the early onset of alcoholism [7]. In general, emesis is preceded with nausea and, in such a condition, it is difficult to administer drug with a glass of water. Hence, it is beneficial to administer such drugs as fast dissolving tablets (FDTs). Ondansetron HCl is an intensely bitter drug; hence, if it is incorporated directly into an FDT, the main objective behind formulation of such a dosage form will definitely be futile [8]. Thus, in the present study, an attempt has been made to mask the taste of Ondansetron HCl and to formulate FDTs with a good mouth feel so as to prepare a “patient-friendly dosage form.”

EXPERIMENTAL SECTION

Ondansetron HCl was obtained as a gift sample from Cadila Pharmaceutical limited, Ahmedabad. Aminoalkyl methacrylate copolymer (Eudragit EPO) was a gift from Degussa India Private Ltd (Mumbai, India). Cross carmellose sodium (Ac-Di-Sol), Crosspovidone were received as a gift sample from Torrent Research Center Ahmedabad, Micro crystalline cellulose, Lactose, D-Mannitol, magnesium stearate were purchased from S.D. Fine Chemicals, Mumbai. Sodium saccharine was purchased from Loba Chemicals Mumbai. All other chemicals used in the study were of analytical grade.

Preparation of drug polymer complex

The drug polymer complex (DPC) was prepared by using different ratio (1:1, 1:3, 1:5) of Ondansetron HCl and Eudragit EPO. A gel containing Ondansetron HCl and Eudragit EPO was prepared by gradual addition of 10 % ethanol using a mechanical stirrer in a glass beaker. The gel was manually extruded through a syringe. The ethanol was evaporated by keeping the extrudates overnight at room temperature. The solidified gel in the shape of string was crushed and sieved through sieve sized 255 µm to make the granules.

Selection of Eudragit EPO for the taste masking of Ondansetron HCl

A simplified dissolution test was performed to determine the optimum fraction of polymer for taste masking of Ondansetron HCl. This is an in-vitro test to evaluate the degree of masking the bitter taste of the fine granules, under the assumption that the fine granules would be held in mouth together with 10 ml of salivary fluid, with weak mixing by the tongue for 60 seconds [9]. The method was as follows: the drug polymer complex (DPC) containing 10 mg of Ondansetron HCl were mixed with 10 ml of simulated salivary fluid (SSF) in a 10 ml syringe by revolving the syringe end to end for 60 seconds. Thereafter solution Ondansetron HCl was filtered and amount of drug release was determined spectrophotometrically at 249 nm. For W1 formulation in-vitro evaluation taste was done by triturating five tablets and powder equivalent to 10 mg of Ondansetron HCl was placed in 10 ml of SSF and shaken for 60 seconds. The amount of drug release was analyzed at 249 nm (Table-1)
Table–1. Drug content and In-Vitro Taste Evaluation of Drug Polymer Complex in SSF

<table>
<thead>
<tr>
<th>Drug Polymer Ratio in DPC</th>
<th>% Drug Dissolve in SSF (pH 6.8)†</th>
<th>% Drug Content in Gastric (pH 1.2)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:1</td>
<td>2.0±0.21</td>
<td>98.42±0.25</td>
</tr>
<tr>
<td>1:3</td>
<td>0.82±0.15</td>
<td>98.72±0.41</td>
</tr>
<tr>
<td>1:5</td>
<td>0.41±0.05</td>
<td>99.12±0.08</td>
</tr>
<tr>
<td>W1 (1:5)</td>
<td>0.43±0.76</td>
<td>99.16±0.18</td>
</tr>
</tbody>
</table>

† Results are the mean of 3 observations ± SD.

Characterization of Drug Polymer Complex

Thermal analysis

DSC analysis was performed using Netzsch DSC 204, Tokyo, Japan. The sample were heated in a sealed aluminium pans at a rate of 10°C per min in a 30 to 300°C temperature under nitrogen flow of 40 ml/min.

Fourier Transform Infrared (FTIR) Spectroscopy

FTIR spectra were obtained on Shimadzu FTIR Model 8400-S spectrometer. The Spectra was recorded as a dispersion of the sample in Potassium Bromide in IR disk (2 mg sample in 200 mg KBr) with the scanning range of 400 to 4000 cm-1 and the resolution was 1 cm -1.

X-ray Diffraction (XRD) studies

X-ray Diffraction analysis was carried out to evaluate the degree of crystallinity. The pure Ondansetron HCl, pure Eudragit EPO, and drug polymer complex (1:5) were subjected to powder XRD (P.W. 1729, X-Ray Generator, Philips, Netherland) at 2θ angles between 2θ and 38θ in increments of 0.4θ.

Drug Content

DPC equivalent to 10 mg of drug was stirred by using magnetic stirrer with 100 ml of 0.1 N HCl for 60 minutes, till the entire drug leached out from complex, than the solution was filter through whatman filter paper. Further solution was diluted with 0.1 N HCl and the drug content was determined spectrophotometrically at 249 nm. (Table 1)

Selection of Superdisintegrants

Before formulation of FDT, the best superdisintegrants among Ac-Di-Sol, and Crosspovidone was screened out. Tablets were prepared in different batches containing a blend of MCC and lactose (1:1) as a diluents and superdisintegrant in various concentrations (Table 2).

Table-2-Disintegration time of Different Super Disintegrants

<table>
<thead>
<tr>
<th>Batch</th>
<th>Disintegrants</th>
<th>Disintegrants % w/w</th>
<th>Diluents % w/w†</th>
<th>Disintegration time, s‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>B1</td>
<td>CCS</td>
<td>4</td>
<td>100</td>
<td>63</td>
</tr>
<tr>
<td>B2</td>
<td>CCS</td>
<td>6</td>
<td>96</td>
<td>38</td>
</tr>
<tr>
<td>B3</td>
<td>CCS</td>
<td>8</td>
<td>94</td>
<td>33</td>
</tr>
<tr>
<td>B4</td>
<td>CRP</td>
<td>4</td>
<td>92</td>
<td>35</td>
</tr>
<tr>
<td>B5</td>
<td>CRP</td>
<td>6</td>
<td>96</td>
<td>45</td>
</tr>
<tr>
<td>B6</td>
<td>CRP</td>
<td>8</td>
<td>94</td>
<td>43</td>
</tr>
<tr>
<td>B7</td>
<td>CRP</td>
<td>8</td>
<td>92</td>
<td>42</td>
</tr>
</tbody>
</table>

CCS- Cross carmellose sodium (Ac-Di-Sol), CRP- Crosspovidone
†1:1 mixture of MCC and lactose; ‡n=3.
Tablet Manufacturing

Preparation of tablet by direct compression method

Fast dissolving tablet of Ondansetron HCl were prepared by direct compression method. All the raw materials were passed through a # 60 sieve prior to mixing. Drug polymer complex (1:5), containing amount equivalent to 10 mg of Ondansetron HCl, was mixed with the other excipients. The powder blend was lubricated with magnesium stearate and compressed on a 10 station mini press tablet machine (CPMD 3-10, Chamunda Pharma Machinery Pvt. Ltd., Ahmedabad, India.) equipped with 9 mm concave punch.

Preparation of Tablet using wet granulation method

Powdered D-Mannitol and pure drug mixed properly with 30% powdered Eudragit EPO. Now this powdered blend converted into wet mass using absolute ethanol. Wet mass than passed through # 30 sieves to make granules. Resulting granules were mixed with 80% lactose and remaining amount of powdered Eudragit EPO and converted in to wet mass using absolute ethanol following sieving through # 30 sieves and resulting granules were dried at room temperature under vacuum. Dried granules were mixed with remaining amount of lactose and passed out from # 40 sieve, mixed with croscarmellose sodium, saccharine Na and mint flavor. Finally lubricated with magnesium stearate and compressed at constant force in to tablets using concave punches (9 mm diameter) in a 10 station mini press tablet machine (CPMD 3-10, Chamunda Pharma Machinery Pvt. Ltd., Ahmedabad, India.)

Table-3 Tablet Formulation

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>mg</th>
<th>Batch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ondansetron HCl</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Eudragit EPO</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>DPC</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>MCC</td>
<td>169</td>
<td>-</td>
</tr>
<tr>
<td>Lactose</td>
<td>-</td>
<td>169</td>
</tr>
<tr>
<td>D-Mannitol</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ac-Di-Sol</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Mag.Stearate</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Saccharin-Na</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Mint flavor</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

Table-4 Physical Properties of Tablet Blend

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Bulk density (g/mL)</th>
<th>Tapped Density (g/mL)</th>
<th>Carr’s Index (%)</th>
<th>Hausner’s Ratio</th>
<th>Angle of Repose(°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.46±0.61</td>
<td>0.51±0.42</td>
<td>8.37±0.19</td>
<td>1.10±0.16</td>
<td>21.56±0.55</td>
</tr>
<tr>
<td>F2</td>
<td>0.26±0.21</td>
<td>0.35±0.35</td>
<td>20.48±0.13</td>
<td>1.34±0.23</td>
<td>23.15±0.54</td>
</tr>
<tr>
<td>F3</td>
<td>0.49±0.16</td>
<td>0.55±0.29</td>
<td>9.92±0.28</td>
<td>1.15±0.13</td>
<td>23.12±0.50</td>
</tr>
<tr>
<td>F4</td>
<td>0.48±0.12</td>
<td>14.72±0.10</td>
<td>1.17±0.01</td>
<td>28.01±0.76</td>
<td>14.72±0.19</td>
</tr>
<tr>
<td>F5</td>
<td>0.52±0.27</td>
<td>0.61±0.05</td>
<td>16.04±0.36</td>
<td>1.16±0.14</td>
<td>29.88±0.56</td>
</tr>
<tr>
<td>F6</td>
<td>0.53±0.02</td>
<td>0.60±0.43</td>
<td>11.03±1.16</td>
<td>1.12±0.21</td>
<td>24.75±0.32</td>
</tr>
<tr>
<td>W1</td>
<td>0.45±0.11</td>
<td>0.68±0.43</td>
<td>30.03±0.12</td>
<td>1.51±0.21</td>
<td>29.75±0.82</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± S.D. (n = 3)

Characterization of powder flow properties [10]

Physical properties such as bulk density, tapped density, compressibility index, and the angle of repose of blend were determined (Table-4). Bulk density was determined by the USP method I; tapped density was determined by USP method II using a tapped density tester (Electrolab, ETD
Percent compressibility and Hausner ratio were calculated using Equations 1 and 2:

\[
\text{Percent compressibility} = \left\{ \frac{(D_t - D_b)}{D_t} \right\} \times 100
\]

(1)

\[
\text{Hausner ratio} = \frac{D_t}{D_b}
\]

(2)

Where, Dt and Db are tapped and bulk densities.

**Characterization of Tablet Properties**

**Uniformity of Mass**

The test was performed as per specification given in I.P.1996 [11] on 20 tablets. The maximum acceptable limit is ± 7.5% deviation of an individual mass from average mass.

**Measurement of Tablet Friability**

Tablet Friability was measured using Roche Friabilator according to specification given in IP 1996. This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm for 4 min. The tablets were dedusted, and the loss in weight caused by the fracture and abrasion was recorded as the % weight loss. Friability below 1% was considered acceptable.

\[
F\% = \left(1 - \frac{W}{W_0}\right) \times 100
\]

Where, \(W_0\) is initial weight of the tablets before the test and \(W\) is the weight of the tablets after test.

**Hardness**

Hardness of the tablet of each formulation was determined using Pfizer hardness tester.

**Uniformity of Drug Content**

The test is obligatory for tablets containing less than 10 mg or less than 10 % w/w of active ingredient [12]. This test was performed as per Indian Pharmacopoeia, 1996. A tablet was crushed and dissolved 1 ml of dilute hydrochloric acid and 30 ml of distill water. This solution was shaken for 15 min. the volume of this solution was made up to 50 ml with distilled water and centrifuged. Five milliliters of the clear supernatant was mixed with 10 ml of 0.1 M hydrochloric acid, and made up to 100 ml with distilled water. The absorption of the solution was determined spectrophotometrically at 249 nm. The same procedure was followed for another nine tablets.

**Wetting time**

A piece of tissue paper folded twice was kept in a culture dish (internal diameter 5.5 cm) containing ~6 mL of purified water. A tablet having a small amount of amaranth powder on the upper surface was placed on the tissue paper. The time required to develop a red color on the upper surface of the tablet was recorded as the wetting time [13].

**In-vitro Disintegration Time**

Disintegration of fast disintegrating tablets is achieved by saliva in the mouth, however amount of saliva in the mouth is limited and no tablet disintegration test was found in USP and IP to simulate in vivo condition. The disintegration time was measured using a modified disintegration method. According to this method, a Petri dish of 10 cm diameter was filled with 10 ml of distilled water, the tablet was carefully places at the center of the Petri dish, and the time necessary for the complete disintegration of the tablet in to fine particles was noted as disintegration time.
In-vitro Dissolution Study
Tablet test condition for the dissolution rate studies were used according USP specification [14] using USP 24, type I apparatus. The dissolution medium was 900 ml of 0.1 N HCl (pH 1.2). The temperature of the dissolution medium and the rate of agitation were maintained at 37±0.5°C and 100 rpm respectively. Aliquots of 10 ml of dissolution medium were withdrawn at specific time interval and the volume replaced by fresh dissolution medium, pre warmed to 37±0.5°C. The drug concentration was determined spectrophotometrically at 249 nm using UV spectrophotometer (Shimadzu S 1700, Japan).

Stability Study
Representative samples (F4, and W1) were placed in a controlled cabinet at 40°C±2°C and 75%±5% RH for 3 months. The effect on various tablet properties such as Friability, hardness and disintegration time was measured. The data were analyzed by one way analysis of variance (ANOVA). A value of P<0.05 was considered as significant.

RESULTS AND DISCUSSION

Characterization of Drug Polymer Complex
Percentage drug content of drug polymer complex and batch W1 in gastric (pH 1.2) was found from 98.42 to 99.16. The drug release in SSF was found least with drug polymer complex ratio (1:5). Thus it is selected as optimized ratio for the development of formulation. In case of batch W1 30% and then 70% of total amount of Eudragit EPO were used to form taste mask granules in (1:5) ratio with drug. The taste masked granules prepared with this Novel wet granulation method showed slightly higher drug release than DPC (1:5) in SSF.

The DSC thermograms of pure Ondansetron HCl, Eudragit EPO, Physical Mixture and drug polymer complex (DPC) are shown in (Figure 1a, 1b, 1c, and 1d). Thermal profile of pure product exhibited a single endothermic effect corresponding to the melting of Ondansetron HCl (T fus 186.477°C, ∆H fus 107.379 J/g) while amorphous nature of polymer. The DSC curve of physical mixture shown progressive broadening and lowering of drug melting temp and concomitant reduction of its enthalpy. In DSC curve of DPC total disappearance of drug melting temperature. These finding suggest the formation of new solid phase with lower degree of crystallinity.
Figure 1b- DSC thermograms of Eudragit EPO

Figure 1c- DSC thermograms of Physical Mixture of Eudragit EPO: Ondansetron HCl

Figure 1d- DSC thermograms of Drug Polymer Complex (DPC)
Figure 2a- FTIR spectra of pure Ondansetron HCl

Figure 2b- FTIR spectra of Eudragit EPO

Figure 2c- FTIR spectra of Physical Mixture of Eudragit EPO: Ondansetron HCl
The FTIR spectrum of pure Ondansetron HCl, Eudragit EPO, Physical Mixture and drug polymer complex (DPC) are shown in (Figure 2a, 2b, 2c, and 2d). The FTIR spectrum of drug and polymer showed no significant shift or reduction in intensity of peaks of Ondansetron HCl. However, the FT-IR spectrum of DPC was found to exhibit some significant difference in the characteristic peaks of Ondansetron HCl, revealing modification of drug environment. As shown in figure a broad band of bonded –OH of Ondansetron HCl was observed from 3491.7 to 3245.31 cm\(^{-1}\). DPC showed the absence of peak at 3491.7 to 3245.31 cm\(^{-1}\) suggest the formation of complexation of drug with polymer.
The x-ray diffractogram of pure Ondansetron HCl, Eudragit EPO, Physical Mixture and drug polymer complex (DPC) are shown in (Figure 3a, 3b, 3c, and 3d). The x-ray diffractogram of Ondansetron HCl confirms its crystalline nature, as evidenced from the number of sharp and intense peak. The diffractogram of polymer (Eudragit EPO) showed diffused peak, indicating the amorphous nature, while the diffraction pattern of drug polymer physical mixture showed simply the sum of characteristic peaks of pure drug and the diffused peaks of polymer, indicating presence of drug in crystalline state. However the diffraction pattern of DPC represents complete disappearance of crystalline peaks of drug especially those situated between 20° and 600 (20). These finding suggest the formation of new solid phase with a lower degree of crystallinity due to complexation.
Selection of Super disintegrants
Initially the tablets containing superdisintegrants in the concentration 4, 6, and 8% w/w were tested for disintegration time. Tablet containing Ac-Di-Sol (6%) shows quick disintegration than crosspovidone. Ac-Di-Sol having excellent disintegration ability. The fibrous nature of Ac-Di-Sol allows intraparticulate as well as extraparticulate wicking of water even at lower concentration. However, Ac-Di-Sol is made by cross-linking (etherification) of sodium carboxymethylcellulose, which greatly reduce its water solubility, while permitting the material to swell and absorb water in amount of several times its own mass without losing its fibrous structure. If Ac-Di-Sol is added in the higher concentration, it makes Ac-Di-Sol more viscous and adhesive [15] this can be the possible reason for the increase of disintegration time of the tablet containing more than 6% of Ac-Di-Sol.

Characterization of Powder Flow Properties
To determine the suitability of the powder blend for tablet compression, all formulation were characterized for various flow properties. The tablet blend for all the batches showed good flow ability (angle of repose < 30°).

Table-5 Characterization of Tablet Properties

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Thickness (mm)</th>
<th>Weight (mg)</th>
<th>Friability (%)</th>
<th>Hardness (kg/cm²)</th>
<th>Disintegration time (s)</th>
<th>Wetting time (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>3.1±0.02</td>
<td>250.3±0.94</td>
<td>0.89±0.28</td>
<td>3.8±0.23</td>
<td>37±1.25</td>
<td>47±1.30</td>
</tr>
<tr>
<td>F2</td>
<td>2.9±0.09</td>
<td>249.8±1.13</td>
<td>0.86±0.16</td>
<td>3.7±0.72</td>
<td>39±1.30</td>
<td>48±1.80</td>
</tr>
<tr>
<td>F3</td>
<td>3.1±0.04</td>
<td>250.0±1.03</td>
<td>0.73±0.83</td>
<td>3.5±0.43</td>
<td>40±2.23</td>
<td>52±2.30</td>
</tr>
<tr>
<td>F4</td>
<td>2.8±0.02</td>
<td>250.6±1.51</td>
<td>0.66±0.35</td>
<td>3.5±0.58</td>
<td>34±1.10</td>
<td>42±1.20</td>
</tr>
<tr>
<td>F5</td>
<td>3.2±0.03</td>
<td>249.8±1.94</td>
<td>0.65±0.24</td>
<td>3.7±0.59</td>
<td>36±1.36</td>
<td>45±1.54</td>
</tr>
<tr>
<td>F6</td>
<td>3.1±0.01</td>
<td>250.4±0.87</td>
<td>0.52±0.29</td>
<td>3.6±0.76</td>
<td>38±1.38</td>
<td>48±1.32</td>
</tr>
<tr>
<td>W1</td>
<td>3.3±0.09</td>
<td>250.2±1.09</td>
<td>0.40±0.12</td>
<td>3.7±0.14</td>
<td>35±1.46</td>
<td>43±1.73</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± S.D. (n = 3)
Characterization of Tablet Properties

Tablets of all the batches were characterized for various tablet properties such as hardness, friability, weight variation, content uniformity, disintegration time and wetting time (Table-5).

It was found that all the tablets prepared by direct compression and wet granulation method described above, independently of their composition, were found to be in acceptable limits for the properties like hardness, friability, weight variation and content uniformity. The friability was observed to be below 1%, which is regarded to be good mechanical resistance.

Tablets of F4 containing lactose and MCC in the ratio 1:1 and 6% Ac-Di-Sol shows faster disintegration and least wetting time with in 34 seconds and 42 seconds respectively. As lactose dissolves quickly it creates pores rapidly encouraging penetration of water into the tablets and this led to quick disintegration of the tablets Batch F3 and F6 containing higher amount of D-Mannitol showed increased wetting and disintegration time. Increase in wetting and disintegration time may be due to increase in polyol quantity in tablet formulation. As polyol are readily soluble in water there exist a competition between mannitol and Ac-Di-Sol for water penetration in to tablet, consequently leading to poor swelling of disintegrant with subsequently delay in disintegration [16].

Disintegration time of batch F5 Containing MCC and D-mannitol in a 1:1 ratio was also slightly more than F4 may be due to lesser penetration of water than F4. The disintegration time and wetting time for batch W1 was found to be 35 and 43 seconds respectively. Disintegration time for the marketed formulation was found to be 102 seconds.

Dissolution Profile

All the formulations prepared with 6 % Ac-Di-Sol release more than 90% drug in 240 seconds. Erosion of tablets is probably an important mechanism of drug release, science very rapid disintegration was noticed with these tablets by visual inspection during dissolution and disintegration studies. From the result of the test, tablet of batch F4 and W1 were considered to possess quick disintegration therefore tested and compared with marketed formulation for dissolution (Figure 4). The dissolution study of batch F4 and W1 revealed rapid release of drug 99% and 98% respectively in 300 seconds at gastric pH 1.2, compared with marketed formulation which had 90 % of drug release in 600 seconds.

![Figure 4- Dissolution profile of batch F4, W1 and Marketed Tablet](image)
Stability Study

Stability study was performed for the formulation F4, and W1 for 3 month as per ICH guidelines, and there was no significant variation observed in physical properties such as hardness, friability and disintegration time of all the formulations (P > 0.05).

CONCLUSION

Result of present study indicates the complexation of Ondansetron HCl and Eudragit EPO can not only mask its bitter taste significantly but also improve the dissolution profile. By employing both the direct compression and wet granulation methods fast dissolving tablets of 250 mg weight with a taste acceptable to patients and sufficient structural integrity could be prepared. From all the super disintegrants studied, tablets containing 6% Ac-Di-Sol gave the highest improvement in disintegration and dissolution profile of Ondansetron HCl. In addition, from stability studies it can be concluded that at 40°C±2°C and 75%±5% RH no significant change in the quality of the tablets during storage is to be expected.

REFERENCES

[12] Indian Pharmacopoeia 1996
ABSTRACT

Fast dissolving tablets of domperidone solid dispersions were prepared by effervescent method with a view to enhance patient compliance. Domperidone is water insoluble antiemetic drug, with problems of variable bioavailability and bioequivalence related to its poor water solubility. The purpose of present investigation to increase the dissolution rate of domperidone by developing domperidone fast dissolving tablets using domperidone solid dispersions, and to determine the influence of amount of superdisintegrant and effervescent materials on tablet disintegration. Differential scanning calorimetry, infrared spectroscopy and scanning electron microscopy were used to characterize the solid state of solid dispersions. Tablets were prepared by conventional direct compression method using Ac-Di-Sol (2-6%) as a superdisintegrant and mixture of sodium bicarbonate (6-18%) and citric acid (3-6%) was used as an effervescent material, along with directly compressible Mannitol to enhance mouth feel. In-vitro dispersion time of the formulation containing Ac-Di-Sol (6%) and mixture of sodium bicarbonate(18%) and citric acid(6%) was found to be 31 seconds and released 88% drug in 5 seconds, whereas marketed tablet released 58% drug in 30 min. Stability study indicated that there were no significant changes in tablet quality was observed.

Keywords: Domperidone, Ac-Di-Sol, Effervescent materials, Scanning electron microscopy, Solid dispersion.

INTRODUCTION

For most of the therapeutic agents oral route still represents the preferred way of administration owing to its several advantages and high patient compliance compare to other routes.

Aqueous solubility is one of the key determinants of new chemical entities as successful drugs; drugs with poor water solubility typically have lower bioavailability. Techniques that have
commonly been used to improve dissolution and bioavailability of poorly water soluble drugs, in general, include micronization, the use of surfactant, and the formation of solid dispersions [1].

Solid dispersion technology is a well known process used to increase the dissolution kinetics and oral absorption of poorly water soluble drugs using water soluble inert carriers [2].

Solid dispersion technique can be applied to increase the dissolution rate by the formation of solid dispersion (SD) with polymeric carrier, such as polyvinyl glycol (PEG) derivatives [3], polyvinyl pyrrolidone (PVP) [4], and hydroxylpropylmethylcellulose [5] PEG 6000 has been used as carrier for increasing the dissolution rate of several poorly water soluble drugs, such as prednisone [6], rofecoxib [7], and diclofenac [8].

Domperidone is a widely used antiemetic, poorly water soluble drug, erratically absorbed in stomach and possess several dissolution problem thus it has poor bioavailability (15%).

In the present investigation, an attempt was made to improve the dissolution rate of domperidone by developing domperidone fast dissolving tablets using solid dispersion technique and to determine the influence of amount of superdisintegrant and effervescent materials on tablet disintegration.

**EXPERIMENTAL SECTION**

**Material and method**
Domperidone (Madley Pharmaceutical Ltd. Daman, India.), Crosscarmellose sodium (Ac-Di-Sol) (Panacea Biotech, Ltd., Lbaru, India). Polyethylene glycol (PEG) 6000, Saccharine-Na, Mannitol, sodium bicarbonate, anhydrous citric acid and magnesium stearate (S.D. Fine chemicals, Mumbai.), and other chemicals and reagent used in the study were obtained commercially and used as received.

**Phase solubility study**
Solubility requirements for domperidone were carried out by a reported method by Higuchi and Connors [9]. An excess amount of domperidone is placed in to a 25 ml glass flask containing different concentration of PEG 6000 in 20 ml of distill water. All flasks were closed with stopper. The content of the suspension was equilibrated by shaking for 72 hours in a thermostatically control water bath at 37°C. After attainment of the equilibrium, the content of each flask was then filter through a 0.45 µm filter. The filtrate was diluted and assayed spectrophotometrically for domperidone content at 284 nm. All solubility measurement was performed in triplicate.

**Preparation of solid dispersion**
Melt method was used to prepare solid dispersions of domperidone with PEG 6000 containing 3 different weight ratio (1:1, 1:3, and 1:5). Domperidone and PEG 6000 were weighed according to these weighed ratios. PEG 6000 was melted at 60°C. In this melted PEG 6000, domperidone was added. It was mixed well and flashed cooled on an ice bath and then stored over night in a dessicator. The prepared solid dispersion was then grounded by using a mortar and pestle, sieved through a mesh 40 and stored over a fused calcium chloride in a dessicator for further use [10-11].
Differential Scanning Calorimetry (DSC)
DSC analysis was performed using Netzsch DSC 204, Tokyo, Japan. The sample were heated in a sealed aluminium pans at a rate of 10°C per min in a 30 to 300°C temperature under nitrogen flow of 40 ml/min.

Fourier Transform Infrared (FTIR) Spectroscopy
FTIR spectra were obtained on Shimadzu FTIR Model 8400-S spectrometer. The Spectra was recorded as a dispersion of the sample in Potassium Bromide in IR disk (2 mg sample in 200 mg KBr) with the scanning range of 400 to 4000 cm⁻¹ and the resolution was 1 cm⁻¹.

Scanning electron microscopy (SEM)
The morphology of domperidone- PEG 6000 system was investigated by means of ESEM TMP with EDAX (Philips, Holland). Samples were previously sputter-coated with a gold layer in order to make them conductive. Pictures were taken at an excitation voltage of 30 kv and a magnification of 1500x

Preparation of tablets by effervescent method
Different domperidone fast dissolving tablets were prepared according to the proportion given (Table 1). All the raw material were passed through a screen (40 mesh) prior to mixing. Powdered 1:5 solid dispersion, containing amount equivalent to 10 mg of domperidone, was mixed with the other excipients. Sodium bicarbonate and anhydrous citric acid were preheated at a temperature of 80°C to remove absorbed/residual moister and were thoroughly mixed in a mortar to get a uniform powder and then mixed with other ingredients. The blend thus obtained was directly compressed on a 10 station mini press tablet machine (CPMD 3-10, Chamunda Pharma Machinery Pvt. Ltd., Ahmedabad, India.) equipped with 9 mm concave punch.

Evaluation of tablet properties
Technological characterization of tablets including hardness, friability, In-vitro dispersion time, wetting time, weight and drug content is shown in (Table 2)

The hardness of the tablets was measured using a Pfizer hardness tester (Sheetal Scientific Industries, Mumbai, India). The limits for crushing strength of the tablets was kept in range of 3-4 kp.

The friability of the tablets was measured using a Roche Friabilator (Electrolab, Ahmedabad, India). Twenty pre weighed tablets were rotated for 4 min at 25 rpm. The tablets were then weighed again, and the percentage of weight loss was calculated the limit of the percent friability was kept below 1%.

In-vitro dispersion time was determined by placing one tablet in a beaker containing 10 ml of pH 6.8 phosphate buffer at 37°C ± 0.5°C and the time required for complete dispersion was determined [12].

Drug content was determined by weighing randomly selected tablets, pulverizing to a fine powder. The weight equivalent to 10 mg domperidone was weighed and dissolved in 5 ml of methanol in volumetric flask using magnetic stirrer, the volume was adjusted to 100 ml with phosphate buffer (pH 6.8) and the solution was filtered. An aliquot of 1.0 ml of solution were diluted to 10 ml phosphate buffer (pH 6.8) in separate volumetric flask. The content in was determined spectrophotometrically at 284 nm.
Table-1. Composition of domperidone fast dissolving tablets

<table>
<thead>
<tr>
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<tr>
<td>SD</td>
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<td>60</td>
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<td>60</td>
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<tr>
<td>Sodium bicarbonate</td>
<td>-</td>
<td>12</td>
<td>24</td>
<td>36</td>
<td>12</td>
<td>24</td>
<td>36</td>
<td>12</td>
<td>24</td>
<td>36</td>
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<tr>
<td>Citric acid</td>
<td>-</td>
<td>6</td>
<td>12</td>
<td>18</td>
<td>6</td>
<td>12</td>
<td>18</td>
<td>6</td>
<td>12</td>
<td>18</td>
</tr>
<tr>
<td>Ac-Di-Sol</td>
<td>-</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>8</td>
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<td>8</td>
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<td>Mannitol</td>
<td>133</td>
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<td>93</td>
<td>75</td>
<td>107</td>
<td>89</td>
<td>71</td>
<td>103</td>
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<td>67</td>
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<td>Saccharine sodium</td>
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<td>3</td>
<td>3</td>
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<td>3</td>
<td>3</td>
<td>3</td>
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<td>3</td>
</tr>
<tr>
<td>Mint flavor</td>
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<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
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<td>2</td>
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<tr>
<td>Magnesium stearate</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

In- Vitro Drug Release
Dissolution studies of domperidone from tablets were performed according to the method described in USP XXIV, using USP II apparatus (paddle method). The dissolution test was performed using 900 ml phosphate buffer pH 6.8, at 37\(^\circ\)C ± 0.5\(^\circ\)C and 50 rpm. Aliquots (5 ml) was removed from the dissolution medium at specific time intervals and was replenished immediatly with same volume of fresh medium, the amount of released domperidone was determined by UV analysis at 284 nm. It was found that PEG 6000 did not interfere with the assay at this wave length. The result presented are mean values of three determinations.

Stability study for Representative sample (EP9) were carried out at 25± 2\(^\circ\)C/60± 5% RH, and 40± 2\(^\circ\)C/75± 5% RH for 6 month. The effect on various tablet properties such as disintegration time, Friability and hardness was measured. The data were analyzed by one way analysis of variance (ANOVA). A value of P< 0.05 was considered as significant.

RESULT AND DISCUSSION

Phase solubility study
The solubility of domperidone in distilled water is found to be 5.35 µg/ml. The influence of the PEG 6000 upon the solubility of Domperidone is presented in (Figure 1). The increase in the solubility was linear (r\(^2\) = 0.997) with respect to the weight fraction of the carrier. At 9% of PEG 6000 the increase in the solubility was ~ 10 fold compare with the pure drug.

![Figure 1-Phase solubility study in distilled water at 37\(^\circ\)C ± 2\(^\circ\)C](image)

The increase in the solubility with increase in PEG 6000 concentration indicates the solvent properties of PEG 6000 for the drug. This feature suggests the A\(_L\)- type phase solubility phase
diagram. The increase in the solubility in the presence of PEG 6000 can probably be explained by increased wettability of domperidone. Indeed, PEG 6000 causes a decrease of the interfacial tension between the drug and the dissolution medium.

**Solid state studies**

The FTIR spectra of domperidone, PEG 6000 and its binary system (1:5) with PEG 6000 are presented in (Figure 2a, 2b and 2c). Pure drug shows sharp characteristic peaks at 2930 cm⁻¹, 1697 cm⁻¹, 1359 cm⁻¹. All the above characteristic peaks appear in the spectra of binary system were independent of the preparation method and there is no significant shift or reduction in intensity of peaks of domperidone was observed.

![Figure 2a](image1)

**Figure 2a- FTIR spectroscopy of pure domperidone**

![Figure 2b](image2)

**Figure 2b- FTIR spectroscopy of PEG 6000**

![Figure 2c](image3)

**Figure 2c- FTIR spectroscopy of drug/PEG 6000 solid dispersion in ratio of 1:5**

Thermal behavior of pure drug, polymer and drug carrier systems are depicted in (Figure 3a, 3b and 3c). Thermal profile of pure drug exhibited a single endothermic effect corresponding to the
melting of domperidone ($T_{\text{fus}}$ 250.71 °C, $\Delta H_{\text{fus}}$ 122.65 J/g) or PEG 6000 ($T_{\text{fus}}$ 65.14 °C, $\Delta H_{\text{fus}}$ 186.5 J/g) respectively. The DSC curve of solid dispersion shown progressive broadening and lowering of drug melting temperature and concomitant reduction of its enthalpy with increasing in carrier content in mixture until total disappearance of drug melting endotherm. This finding could be considered indicative of drug amorphization as a consequence of interaction between components [13]. It also shows the progressive drug dissolution in the melted carrier before achieving its melting carrier, as was previously observed for other the drug-PEG combination [14-15].
Figure 3c- Differential Scanning Calorimetry of drug/PEG 6000 solid dispersion in ratio of 1:5 (Figure 4a, 4b and 4c) shows SEM images of the pure component and SD system. PEG 6000 (Figure 4b) existed in a crystalline mixture of sooth-surfaced particle with smaller particle, while domperidone (Figure 4a) existed in small irregular particle. On the contrary, SD (1:5) (Figure 4c) consisted of more spherical particles of rather irregular surface. In the case of SD (1:5), at the high polymer ratio, particles presented a surface morphology similar to that of pure PEG 6000. In these monograph, it is impossible to distinguish the presence of domperidone crystals among the PEG particles. The novel arrangement between domperidone and PEG.

Figure 4a- Scanning Electron Microscopy of pure domperidone
Particles might be responsible for the enhance drug dissolution rate found for SD system, in comparison with the pure domperidone. To our knowledge, we are the first to attempt to characterize the morphology of domperidone: PEG 6000 system.
Evaluation of tablet properties
The friability, hardness, disintegration time, wetting time, drug content and weight of formulated tablets are described in (Table 2). Hardness of all the formulation was in range of 3.3 -3.5 kg/cm². Friability of all the formulation was below 1% indicates that the tablets had good mechanical resistance. Drug content was found to be in range of 100-103%. The weight variation results revealed that average % deviation of 20 tablets of each formulation was less than ±7.5%, which provide good uniformity in all formulations.

In-vitro dispersion time for the fast dissolving tablets, prepared with Ac-Di-Sol (6%) and mixture of sodium bicarbonate (18%) and citric acid (6%) was found to be 31 seconds, while disintegration time of control formulation EP0 was found to be 112 seconds. Ac-Di-Sol is a ‘superdisintegrant’ of excellent disintegration ability. It swells to a great extent when in contact with water, by a water wicking mechanism; this may be the possible reason for decrease in the disintegration time with Ac-Di-Sol (6%). Results obtained revealed that the In-vitro dispersion time is strongly dependent on the concentration of superdisintegrants and effervescent material. As the concentration of both Ac-Di-Sol and mixture of sodium bicarbonate and citric acid increases, In-vitro dispersion time decreases.

Table-2. Technological characterization of domperidone fast dissolving tablets

<table>
<thead>
<tr>
<th>Formulation</th>
<th>In-vitro dispersion time (seconds)</th>
<th>Wetting time (seconds)</th>
<th>Hardness (kg/cm²)</th>
<th>Friability (%)</th>
<th>Drug content (%)</th>
<th>Weight (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EP0</td>
<td>112 (1.8)</td>
<td>108 (1.9)</td>
<td>3.5 (1.0)</td>
<td>0.43 (0.7)</td>
<td>100.4 (1.2)</td>
<td>202</td>
</tr>
<tr>
<td>EP1</td>
<td>53 (1.2)</td>
<td>51 (1.2)</td>
<td>3.3 (0.2)</td>
<td>0.51 (0.2)</td>
<td>101.2 (1.0)</td>
<td>200</td>
</tr>
<tr>
<td>EP2</td>
<td>50 (0.8)</td>
<td>46 (1.1)</td>
<td>3.3 (0.8)</td>
<td>0.46 (0.5)</td>
<td>100.5 (0.8)</td>
<td>198</td>
</tr>
<tr>
<td>EP3</td>
<td>46 (1.1)</td>
<td>42 (1.0)</td>
<td>3.4 (0.6)</td>
<td>0.43 (0.4)</td>
<td>103.2 (0.6)</td>
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</tr>
<tr>
<td>EP4</td>
<td>44 (1.3)</td>
<td>41 (1.4)</td>
<td>3.5 (0.1)</td>
<td>0.53 (1.1)</td>
<td>102.2 (1.0)</td>
<td>201</td>
</tr>
<tr>
<td>EP5</td>
<td>42 (1.6)</td>
<td>39 (1.1)</td>
<td>3.4 (0.4)</td>
<td>0.49 (0.9)</td>
<td>101.3 (1.2)</td>
<td>201</td>
</tr>
<tr>
<td>EP6</td>
<td>40 (0.6)</td>
<td>36 (1.2)</td>
<td>3.5 (0.5)</td>
<td>0.42 (0.2)</td>
<td>103.2 (2.0)</td>
<td>202</td>
</tr>
<tr>
<td>EP7</td>
<td>38 (1.4)</td>
<td>34 (1.3)</td>
<td>3.4 (0.7)</td>
<td>0.54 (0.8)</td>
<td>103.2 (0.4)</td>
<td>202</td>
</tr>
<tr>
<td>EP8</td>
<td>35 (1.0)</td>
<td>31 (1.0)</td>
<td>3.5 (0.7)</td>
<td>0.43 (0.7)</td>
<td>102.5 (0.5)</td>
<td>200</td>
</tr>
<tr>
<td>EP9</td>
<td>31 (2.7)</td>
<td>28 (1.23)</td>
<td>3.5 (0.6)</td>
<td>0.40 (1.0)</td>
<td>102.4 (0.6)</td>
<td>201</td>
</tr>
</tbody>
</table>

In vitro drug release from all the formulations containing domperidone PEG 6000(1:5) solid dispersion and effervescent material were more than 81% in 5 min. In-vitro drug release profile of formulation EP9 was more than 88% in 5 min compared with marketed tablet 58% in 30 min. (Figure 5), revealed that formulation of tablet using solid dispersion with PEG 6000 increased the dissolution of drug.

The result of stability testing indicate that there is no significant change in disintegration time, friability and hardness at 25± 2° C/60± 5% RH, and 40± 2° C/75± 5% RH was observed.
CONCLUSION

Fast dissolving tablet of domperidone can be prepared by effervescent method using solid dispersion of drug instead of drug as such. Proper selection of drug/carrier ratio and tablet additives can provide rapid tablet disintegration and release of the drug. The present study showed the suitability of PEG 6000 as a carrier for the preparation of domperidone solid dispersions. As demonstrated by both DSC and SEM, the amorphization of domperidone offered an explanation of better dissolution rate from its solid dispersions. In the present study, use of solid dispersion containing domperidone/PEG 6000 (1:5), Ac-Di-Sol 6% and mixture of sodium bicarbonate(18%) and citric acid(6%) in the tablets disintegrates in 31 seconds, and released 88% drug in 5 min. It’s therefore proposed that such tablets could be used in the emergency treatment of emesis.

REFERENCES

[6] L Dario; GB Maria; CL Maria; JS Claudio. AAPS PharmSciTech., 2007, 8(4), E1-E7.
DEVELOPMENT AND EVALUATION OF FAST DISSOLVING TABLETS USING DOMPERIDONE: PEG 6000 SOLID DISPERSIONS

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ABSTRACT
Domperidone is water insoluble anti emetic drug, with problems of variable bioavailability and bio- in equivalence related to its poor water solubility. The purpose of present investigation to increase the dissolution rate of domperidone by developing domperidone tablet, allowing fast, reproducible and complete drug dissolution using solid dispersions of domperidone. Tablets were prepared by conventional wet granulation and direct compression method. Crosscarmellose sodium (Ac-Di-Sol) and Crosspovidone were used as superdisintegrant to achieve rapid disintegration of tablet. Tablet developed in this study disintegrated 50 seconds (wet granulation) and 49 (direct compression) seconds, and released 80 % and 83% drug in 5 min. whereas marketed tablet released 58% drug in 30 min. This study indicated that fast dissolving tablet can be prepared by conventional methods utilizing the existing infrastructure of tablet manufacturing.

Keywords: Domperidone, Fast dissolving tablet, Scanning electron microscopy, Solid dispersion.

INTRODUCTION
Oral route of drug administration is perhaps the most appealing route for the delivery of drugs. Aqueous solubility is one of the key determinants of new chemical entities as successful drugs; drugs with poor water solubility typically have lower bioavailability. Techniques that have commonly been used to improve dissolution and bioavailability of poorly water soluble drugs, in general, include micronization, the use of surfactant, and the formation of solid dispersions.1

Drug amorphization by spray-drying was experimented as a method of increasing the drug dissolution rate, but the amorphous form was instable and rapidly deactivated into the crystalline form.2

Solid dispersion technology is a well known process used to increase the dissolution kinetics and oral absorption of poorly water soluble drugs using water soluble inert carriers.3

Solid dispersion technique can be applied to increase the dissolution rate by the formation of solid dispersion (SD) with polymeric carrier, such as polyvinyl glycol (PEG) derivatives,4 polyvinyl pyrrolidone (PVP),5 and hydroxypolymethyl cellulose.6 PEG 6000 has been used as carrier for increasing the dissolution rate of several poorly water soluble drugs, such as prednisone,7 rofecoib,8 and paracetamol.9

Domperidone exhibits poor aqueous solubility that produces erratic and delayed absorption when administered orally. Rapid absorption of drug requires rapid dissolution, which in turn depends on higher aqueous solubility.

The present study aims to formulate such a tablet that disintegrates rapidly and provides rapid dissolution of drug.

MATERIALS AND METHODS
Domperidone (Madley Pharmaceutical Ltd. Daman, India.), Crosspovidone and Crosscarmellose sodium (Ac-Di-Sol) (Panacea Biotech, Ltd., Larlu, India), Polyethylene glycol (PEG) 6000, Starch, Saccharine-Na, D-Mannitol, Lactose monohydrate (S.D. Fine chemicals, Mumbai), and other chemicals and reagent used in the study were obtained commercially and used as received.

Methods
Preparation of solid dispersion
Solid dispersions of domperidone: PEG 6000 in different weight ratio (1:1, 1:5, and 1:9) was prepared and characterized as per the previously published method10

Preparation of tablets by wet granulation method
Raw materials were passed through a No. 44 screen. Domperidone (as such or in solid dispersion), microcrystalline cellulose, lactose and intra-granular fraction of crosscarmellose sodium (Ac-Di-Sol) were mixed and converted in to a wet mass with starch paste. Wet mass then passed through sieve No. 18 and resulting granules were dried in hot air oven at 40 °C for 2 h. following sieving through No. 22 sieve, granules were mixed with extra granular fraction of crosscarmellose sodium and magnesium stearate and compressed at constant force into tablets using concave punches (9 mm diameter) in a 10 station mini press tablet machine (CPMD 3-10, Chamunda Pharma Machinery Pvt. Ltd., Ahmedabad, India.)

Preparation of tablets by direct compression method
The direct compression technique was used for the tablet preparation. All the raw material were passed through a screen (40 mesh) prior to mixing. Powdered 1.5 solid dispersion, containing amount equivalent to 10 mg of domperidone, was mixed with the other excipients and compressed on a 10 station mini press tablet machine (CPMD 3-10, Chamunda Pharma Machinery Pvt. Ltd., Ahmedabad, India.) equipped with 9 mm concave punch.

Table 1: Composition of Domperidone Fast dissolving tablet by wet granulation method

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Batch</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F1</td>
</tr>
<tr>
<td>Domperidone</td>
<td>10</td>
</tr>
<tr>
<td>SD</td>
<td>20</td>
</tr>
<tr>
<td>Crosscarmellose sodium</td>
<td>0</td>
</tr>
<tr>
<td>Starch</td>
<td></td>
</tr>
<tr>
<td>Micro crystalline cellulose</td>
<td>100</td>
</tr>
<tr>
<td>Lactose</td>
<td>126.5</td>
</tr>
<tr>
<td>Na-Saccharin</td>
<td>2.5</td>
</tr>
<tr>
<td>Mag. Stearate</td>
<td>1</td>
</tr>
</tbody>
</table>
Dissolution tests of domperidone from tablets were performed in a paddle apparatus (paddle method). The dissolution test was performed in USP XXIV using USP II apparatus (paddle method). The dissolution test was performed according to the method described in USP XXIV, using USP II apparatus (paddle method). The dissolution test was performed using 900 ml phosphate buffer pH 6.8 and the solution was filtered. An aliquot of 1.0 ml of solution was diluted to 10 ml phosphate buffer (pH 6.8) in separate volumetric flask. The content in was determined spectrophotometrically at 284 nm.

In vitro Drug Release

Dissolution studies of domperidone from tablets were performed according to the method described in USP XXIV, using USP II apparatus (paddle method). The dissolution test was performed using 900 ml phosphate buffer pH 6.8 and the solution was filtered. An aliquot of 1.0 ml of solution was diluted to 10 ml phosphate buffer (pH 6.8) in separate volumetric flask. The content in was determined spectrophotometrically at 284 nm.

Evaluation of tablet properties

The hardness of the tablets was measured using a Pfizer hardness tester (SHEETAL SCIENTIFIC INDUSTRIES, MUMBAI, INDIA). The limits for crushing strength of the tablets was kept in range of 3-4 kP. The hardness of the tablets was measured using a Roche Friabilator (ELECTROLAB, AHMEDABAD, INDIA). Twenty pre-weighed tablets were rotated for 4 min at 25 rpm. The tablets were then weighed again, and the percentage of weight loss was calculated. The limit of the percent friability was kept below 1%.

The disintegration time was noted using a modified disintegration method. According to this method, a petri dish of 10-cm diameter was filled with 10 ml of distilled water, the tablet was carefully placed at the center of the petri dish, and the time necessary for the complete disintegration of tablet into fine particles was noted as disintegration time.

Drug content

Randomly selected tablets were weighed and powdered in a glass mortar pestle. The weight equivalent to 10 mg domperidone was weighed and dissolved in 5 ml of methanol in volumetric flask using magnetic stirrer, the volume was adjusted to 100 ml with phosphate buffer (pH 6.8) in separate volumetric flask. The disintegration time was noted using a modified disintegration method. According to this method, a petri dish of 10-cm diameter was filled with 10 ml of distilled water, the tablet was carefully placed at the center of the petri dish, and the time necessary for the complete disintegration of tablet into fine particles was noted as disintegration time.

Stability study

Representative samples (F6, and P3) were placed in a controlled cabinet at 40°C ± 2°C and 75% ± 5% RH for 3 months. The content of domperidone was analyzed monthly by UV spectroscopy. The data were analyzed by one way analysis of variance (ANOVA). A value of P<0.05 was considered as significant.

RESULT AND DISCUSSION

Evaluation of tablet properties

The friability, hardness, disintegration time, wetting time, drug content and weight of formulated tablets are described in Table 3. All the parameters are within the acceptable range. Good uniformity in drug content was found amongst different batches. In wet granulation method, tablets prepared using starch disintegrated with in 25 second and release 9% and 44% drug in 5 minutes and 30 minutes respectively (Fig. 1). Incorporation of crosscarmellose sodium (6%) as superdisintegrant increased the disintegration time of tablets with the carrier could be responsible for improvement in solubilization and consequent dissolution of drug.

Crosscarmellose-Na is made from sodium carboxymethylcellulose by a cross linking reaction (estriification), which greatly reduce water solubility of sodium carboxymethylcellulose while permitting material to absorb water and swell many times its weight with out losing individual fiber integrity.11 When Crosscarmellose-Na is added to a tablet formulation at higher concentration, absorption of water may cause an increase in viscosity of liquid within tablet and may delay further penetration of water. As water absorption is an important step in disintegration process, increase in Crosscarmellose-Na concentration exhibited a delayed tendency in tablet disintegration. Tablets prepared with starch and Crosscarmellose-Na (6%) exhibited shortest disintegration time but having poor release rate (Fig. 1) and almost equal to the tablets prepared without Crosscarmellose-Na. Prolong dissolution time could be correlated with poor aqueous solubility of poorly water soluble drugs. In the present study, PEG 6000 was used to prepare solid dispersion of domperidone. Tablets prepared with solid dispersion of drug and PEG 6000 (1:1), disintegrated in 38 seconds and released more than 50 % drug in 5 minutes (Fig. 2). When the ratio of PEG 6000 and drug in solid dispersion was increased, disintegration time of tablets also increased although release of drug was found to be faster (Fig. 2). Drug release from tablets prepared with solid dispersion of drug and PEG 6000 in ratio of (1:5) and (1:9) were found to be 80% and 92% respectively in 5 minutes (Fig. 2). Drug release from formulation F5, F6 and F7 was found to be significant (P<0.05). This shows that when the ratio of PEG 6000 and drug in solid dispersion increases, the rate of drug release increases significantly. It was found that the disintegration time was increased with increasing in the concentration of PEG 6000 and for the formulation F6 and F7 it was found to be 58 and 108 seconds respectively. Previous studies indicated that PEG 4000 and PEG 6000 prolonged the disintegration time of tablet. When compare amongst various formulations, tablets containing drug: PEG 6000 (1:5) and 6 % crosscarmellose sodium were found to be optimum in relation to rapid disintegration and dissolution.

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In vitro Drug Release

Dissolution studies of domperidone from tablets were performed according to the method described in USP XXIV, using USP II apparatus (paddle method). The dissolution test was performed using 900 ml phosphate buffer pH 6.8 and the solution was filtered. An aliquot of 1.0 ml of solution was diluted to 10 ml phosphate buffer (pH 6.8) in separate volumetric flask. The content in was determined spectrophotometrically at 284 nm.

Table 2: Composition of Domperidone Fast dissolving tablet by direct compression method

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Formulation P1/P2/P3 (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug –polymer solid dispersion (1:5)</td>
<td>60</td>
</tr>
<tr>
<td>Crosspovidone</td>
<td>5/10/15</td>
</tr>
<tr>
<td>D-Mannitol</td>
<td>50</td>
</tr>
<tr>
<td>Lactose monohydrate</td>
<td>130/125/120</td>
</tr>
<tr>
<td>Na-Saccharin</td>
<td>2.5</td>
</tr>
<tr>
<td>Mag. sterile</td>
<td>2.5</td>
</tr>
</tbody>
</table>

Optimized formulation (F6, P3), on compare with a commercial marketed tablet of domperidone, exhibited rapid drug dissolution (Fig. 2, and 3).

Stability study

Stability study was performed for the formulation F6, and P3 for 3 months as per ICH guidelines, and there was no significant variation observed in the drug content of all the formulations (P> 0.05).
Table 3: Technological Characterization of domperidone fast dissolving tablets

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Formulations</th>
<th>Weight (mg)</th>
<th>Friability (%)</th>
<th>Hardness (kg/cm²)</th>
<th>Disintegration time (sec)</th>
<th>Drug content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F1</td>
<td>249.8±3.23</td>
<td>0.51±0.05</td>
<td>3.0±0.25</td>
<td>25±0.81</td>
<td>99.72±1.12</td>
</tr>
<tr>
<td></td>
<td>F2</td>
<td>249.8±3.52</td>
<td>0.58±0.04</td>
<td>3.0±0.12</td>
<td>17±0.12</td>
<td>99.29±1.04</td>
</tr>
<tr>
<td></td>
<td>F3</td>
<td>248.1±2.67</td>
<td>0.57±0.06</td>
<td>3.1±0.16</td>
<td>12±0.58</td>
<td>98.32±1.21</td>
</tr>
<tr>
<td></td>
<td>F4</td>
<td>249.2±4.42</td>
<td>0.62±0.042</td>
<td>3.0±0.18</td>
<td>22±0.24</td>
<td>99.08±1.34</td>
</tr>
<tr>
<td></td>
<td>F5</td>
<td>250.8±3.32</td>
<td>0.63±0.039</td>
<td>3.4±0.13</td>
<td>38±0.17</td>
<td>100.32±1.02</td>
</tr>
<tr>
<td></td>
<td>F6</td>
<td>249.1±2.73</td>
<td>0.64±0.051</td>
<td>3.6±0.15</td>
<td>58±0.25</td>
<td>99.87±1.43</td>
</tr>
<tr>
<td></td>
<td>F7</td>
<td>249.9±1.7</td>
<td>0.60±0.049</td>
<td>3.8±0.13</td>
<td>108±0.94</td>
<td>101.02±1.14</td>
</tr>
<tr>
<td></td>
<td>P1</td>
<td>249.8±4.23</td>
<td>0.61±0.05</td>
<td>3.5±0.12</td>
<td>60±0.23</td>
<td>100.08±1.21</td>
</tr>
<tr>
<td></td>
<td>P2</td>
<td>249.8±3.52</td>
<td>0.48±0.04</td>
<td>3.4±0.52</td>
<td>54±0.28</td>
<td>99.85±1.43</td>
</tr>
<tr>
<td></td>
<td>P3</td>
<td>247.1±2.67</td>
<td>0.47±0.06</td>
<td>3.5±0.16</td>
<td>49±1.25</td>
<td>101.01±1.35</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± S.D. (n = 3)

Fig. 1: Cumulative % drug release of formulation F1, F2, F3 and F4

Fig. 2: Cumulative % drug release of formulation F5, F6, F7 and Marketed tablet

Fig. 3: Cumulative % drug release of formulation P1, P2, P3 and Marketed tablet
CONCLUSION
Fast dissolving tablet of domperidone can be prepared by existing tablet manufacturing technologies such as wet granulation and direct compression method using solid dispersion of drug instead of drug as such. The present study showed the suitability of PEG 6000 as a carrier for the preparation of domperidone solid dispersions. In the present study, use of solid dispersion containing domperidone/PEG 6000 (1:5) in the tablets prepared by wet granulation and direct compression disintegrates in 58 and 47 seconds, and released 80% and 83% drug in 5 min. It’s therefore proposed that the dissolution rate of domperidone can be enhanced to a greater extent, which gives quick relief from emesis.

REFERENCE
DESIGN, DEVELOPMENT AND OPTIMIZATION OF FAST DISSOLVING TABLET OF ONDANSETRON HCl USING MANNITOL WITH CAMPHOR, A SUBLIMING MATERIAL

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1Maharishi Arvind Institute of Pharmacy, Jaipur, Rajasthan, India, 2APL Research Centre, A Division of Aurbindo Pharma Ltd., Hyderabad, India, 3K.B. Institute of Pharmaceutical Education and Research, Gndhinagar, Gujarat, India. Email: shailubhatt@gmail.com

ABSTRACT
Objective: The crucial aspect of present work was to develop fast dissolving tablet of Ondansetron HCl with rapid disintegration, adequate hardness and pleasant mouth feel.

Method: In the present work response surface approach was applied to investigate main and interaction effects of formulation parameters in optimizing fast dissolving tablet (FDT) formulation using subliming material (camphor) and mannitol. The variables studied were mannitol (X1) and camphor (X2). Tablets were prepared using sublimation technique.

Results: It was observed that the responses (disintegration time and hardness) were strongly affected by both the factors studied. The statistical models were validated and can be successfully used to prepare and optimized fast dissolving tablets of Ondansetron HCl with rapid disintegration (31 seconds) and excellent hardness (4.0 kg/cm²).

Conclusion: It was concluded that fast dissolving tablet with high mechanical strength and rapid disintegration without the use of supersolvent could be prepared, which provide better patient compliance.

Keywords: Ondansetron HCl, Fast dissolving tablet, Optimization, Factorial design, Sublimation technique.

INTRODUCTION
Tablets and capsules constitute a major portion of currently available drug delivery systems. However, many patient groups such as the elderly, children, the mentally retarded, or uncooperative, nauseated, or patients with dysphagia, have difficulty in swallowing these dosage forms. Fast dissolving tablets (FDT) are very beneficial for the patient with difficulties in swallowing and in condition where excess of water is difficult. These dosage forms when placed in the mouth disintegrate in the oral cavity within 60 seconds without the need for water, thus providing optimal convenience to the patient [1-2]. Their characteristic advantages such as administration without water, anywhere, anytime lead to their suitability to geriatric and paediatric patients, they are also suitable for the mentally ill, the bedridden and patients who do not have easy access to water and also the bioavailability of drug is significantly greater than those observed from conventional tablet dosage form [3].

Innovators and inventor companies have given these tablets various names such as rapidly disintegrating, mouth dissolve, quick dissolving, fast melting, or oro-disperse tablets [4-5].

This dosage form combines the advantages of dry and liquid formulations. The technologies should allow high drug loading, have an acceptable taste, offer a pleasant mouth feeling and leave minimal residue in the mouth after oral administration. The advantages of fast dissolving tablets are recognized by industry and patients, since there are several products available on the market. These products have a number of drawbacks, including the manufacturing methods used and the mechanical strength. Three techniques are mainly applied to formulate these tablets, namely freeze-drying moulding and direct compression. Lyophilized tablets show a very porous structure, which causes quick penetration of saliva into the pores when placed in the oral cavity [6-7]. The main disadvantages of this dosage form are, in addition to the cost intensive production process, the lack of physical resistance in standard blister packs and formulation problems caused by using highly water-soluble excipients. Further for systematic development of the formulation, an optimization technique based on response surface methodology was utilized. Response surface methodology can be defined as a statistical method that uses quantitative data from appropriate experiments to determine and simultaneously solve multivariate equations. It is generally used to determine the optimum combination of factors that yield a desired response and describes the response near the optimum. This methodology was used in the present study to optimize the variables affecting the formulation.

MATERIAL AND METHOD
Ondansetron HCl was obtained as a gift sample from Cadila Pharmaceutical limited, Ahmedabad. Camphor was obtained from a local ayurvedic pharmacy. Mannitol, lactose and magnesium stearate were purchased from S.D. Fine Chemicals, Mumbai. All other chemicals used in the study were of analytical reagent grade.

Methods
Preparation of drug polymer complex
The drug polymer complex (DPC) was prepared and characterized as per previously published method [8].

Formulation development
DPC was used to prepare FDT by direct compression technique. Composition of tablet is mentioned in (Table 1). All the raw materials were passed through a 80 mesh prior to mixing. Drug polymer complex (1:5), containing amount equivalent to 10 mg of Ondansetron HCl, was mixed with the other excipients. The powder blend was lubricated with magnesium stearate and compressed on a 10 station mini press tablet machine (CPMD 3-10, ChamundaPharma Machinery Pvt. Ltd., Ahmedabad, India.) equipped with 9 mm
concealed punch. The tablets were dried in a vacuum oven for 4 h at a temperature of 60 °C and at a pressure of 300 mm Hg.

**Table 1:** It shows typical formula for fast dissolving tablet of Ondansetron HCl

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Quantity (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPC</td>
<td>24</td>
</tr>
<tr>
<td>Camphor</td>
<td>0-40</td>
</tr>
<tr>
<td>Mannitol</td>
<td>10-50</td>
</tr>
<tr>
<td>Mag stearate</td>
<td>1.5</td>
</tr>
<tr>
<td>Lactose</td>
<td>q.s. to 250</td>
</tr>
</tbody>
</table>

*Tablet weight = 250 mg

**Experimental design of Ondansetron HCl fast dissolving tablets**

A randomized 3 level full factorial design using two factors was adopted to systematically study the formulation of FDT of Ondansetron HCl. A total of 12 experimental run with 3 centre points were performed at all possible combination (Table 3). The amount of Mannitol (X1) and concentration subliming agent, camphor (X2) were selected as independent variable (Table 2). The disintegration time and hardness were selected as dependent variable. The responses were analysed for analysis of variance (ANOVA) using Design Expert version8.0. Statistical models were generated for each response parameter. The models were tested for significance.

**Table 2:** It shows variables in 3 level full factorial design

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>Levels (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>X1=Mannitol</td>
<td>Low (-1)</td>
</tr>
<tr>
<td></td>
<td>Middle (0)</td>
</tr>
<tr>
<td></td>
<td>High (+1)</td>
</tr>
<tr>
<td>X2=Camphor</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>50</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dependent variable</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y1=Disintegration time (seconds)</td>
<td></td>
</tr>
<tr>
<td>Y2=Hardness (kg/cm²)</td>
<td></td>
</tr>
</tbody>
</table>

**Validation of statistical model**

Levels of both the factors were selected at two different points and responses predicted by the statistical models were calculated. Fast dissolving tablets were prepared using these levels and responses were measured practically. The predicted responses were compared against observed responses and closeness between them was checked.

**Table 3:** It shows matrix of full factorial design and responses for each experimental run

<table>
<thead>
<tr>
<th>Run</th>
<th>X1: Mannitol (%)</th>
<th>X2: Camphor (%)</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-1</td>
<td>-1</td>
<td>35±0.89</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>0</td>
<td>23±0.57</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>0</td>
<td>23±0.73</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>-1</td>
<td>33±0.59</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>0</td>
<td>28±0.96</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>0</td>
<td>8±0.62</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
<td>1</td>
<td>23±0.71</td>
</tr>
<tr>
<td>8</td>
<td>0</td>
<td>1</td>
<td>11±0.67</td>
</tr>
<tr>
<td>9</td>
<td>-1</td>
<td>1</td>
<td>12±0.91</td>
</tr>
<tr>
<td>10</td>
<td>0</td>
<td>0</td>
<td>22±0.85</td>
</tr>
<tr>
<td>11</td>
<td>-1</td>
<td>0</td>
<td>15±0.89</td>
</tr>
<tr>
<td>12</td>
<td>1</td>
<td>-1</td>
<td>32±0.90</td>
</tr>
</tbody>
</table>

*Data are expressed as means±SD (standard deviation), n=3.

**Response surface plots**

Response surface plots were generated for each response to study the effect of both factors on each response.

**Evaluation of prepared tablets**

**Uniformity of Mass**

The test was performed as per specification given in IP [1996] on 20 tablets. The maximum acceptable limit is ± 5% deviation of an individual mass from average mass.

**Friability**

Twenty tablets were weighed and placed in a Roche friabilator and the equipment was recorded at 25 rpm for 4 min. The tablets were taken out, de dusted, and reweighed. The percentage friability of the tablets was calculated using the following equation [9]

\[ F \% = \left( 1 - \frac{W}{W_0} \right) \times 100 \]

Where, \( W_0 \) is initial weight of the tablets before the test and \( W \) is the weight of the tablets after test.

**Hardness**

Hardness of the tablet of each formulation was determined using Pfizer hardness tester.

**Wetting time**

A piece of tissue paper folded twice was kept in a culture dish (internal diameter 5.5 cm) containing 6 mL of purified water. A tablet having a small amount of amaranth powder on the upper surface was placed on the tissue paper. The time required to develop a red colour on the upper surface of the tablet was recorded as the wetting time [10].

**Disintegration time**

Disintegration of fast dissolving tablets is achieved by saliva in the mouth, however amount of saliva in the mouth is limited and no tablet disintegration test was found in USP and IP to simulate in vivo condition. The disintegration time was measured using a modified disintegration method. According to this method, a Petri dish of 10 cm diameter was filled with 10 ml of distilled water, the tablet was carefully placed at the centre of the Petri dish, and the time necessary for the complete disintegration of the tablet in to fine particles was noted as disintegration time [11].

**Dissolution studies**

Tablet test condition for the dissolution rate studies were used according USP specification [12] using USP 24, type II apparatus. The dissolution medium was 900 ml of 0.1 N HCl (pH 1.2). The temperature of the dissolution medium and the rate of agitation were maintained at 37±0.5°C and 50 rpm respectively. Aliquots of 10 ml of dissolution medium were withdrawn at specific time interval and the volume replaced by fresh dissolution medium, pre warmed to 37±0.5°C. The drug concentration was determined spectrophotometrically at 249 nm using UV spectrophotometer (Shimazdu S 1700, Japan).

**Scanning electron microscopy (SEM)**

The optimized tablet was also observed by scanning electron microscope (ESEM TMP with EDAX, Philips, Holland). Pictures were taken at an excitation voltage of 30 kv and a magnification of 120 X.
RESULT AND DISCUSSION

Evaluation of tablet

The outcomes of various evaluation parameters are shown in (Table 4). In-vitro drug release profile of all factorial batches and optimized batch showed in (Fig. 1) and it was found to be more than 95% in 4 minutes than compare to 90% in 10 minutes for marketed product (ONDEM MD8). The disintegration time of FDTS should be less than 60 s and ideally between 20 and 40 s. Thus, it was observed that the simple addition of a superdisintegrant could not obtain the most desirable feature of an FDT, and that another suitable technique would have to be used. The vacuum-drying technique was then adopted to create a porous structure in the tablets. In this technique, subliming agent (camphor) was used to increase the tablets' porosity. The porous structure induced in the tablet matrix due to the sublimation of camphor was responsible for faster water uptake, thus facilitating rapid disintegration. On the other hand higher concentration of camphor formed fragile tablet, thus there was a need to optimize the concentration of camphor. Mannitol was used to increase the mechanical strength and provide pleasant mouth feel.

Table 4: It shows characterization of fast dissolving tablets

<table>
<thead>
<tr>
<th>Parameters* Formulations</th>
<th>Weight (mg)</th>
<th>Friability (%)</th>
<th>Wetting time (Seconds)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OV1</td>
<td>249.5±1.25</td>
<td>0.32±0.54</td>
<td>25±1.48</td>
</tr>
<tr>
<td>OV2</td>
<td>250.2±1.47</td>
<td>0.64±0.47</td>
<td>14±1.59</td>
</tr>
<tr>
<td>OV3</td>
<td>251±1.59</td>
<td>0.67±0.53</td>
<td>13±1.28</td>
</tr>
<tr>
<td>OV4</td>
<td>248.5±1.25</td>
<td>0.58±0.27</td>
<td>19±1.25</td>
</tr>
<tr>
<td>OV5</td>
<td>250±1.39</td>
<td>1.2±0.39</td>
<td>4±0.29</td>
</tr>
<tr>
<td>OV6</td>
<td>249.5±1.28</td>
<td>0.56±0.58</td>
<td>14±1.44</td>
</tr>
<tr>
<td>OV7</td>
<td>250±1.45</td>
<td>1.8±0.37</td>
<td>5±1.57</td>
</tr>
<tr>
<td>OV8</td>
<td>250±1.28</td>
<td>1.6±0.48</td>
<td>5.5±1.04</td>
</tr>
<tr>
<td>OV9</td>
<td>250.5±1.39</td>
<td>62±0.47</td>
<td>12±1.43</td>
</tr>
<tr>
<td>OV10</td>
<td>249.8±1.40</td>
<td>72±0.53</td>
<td>7±1.41</td>
</tr>
<tr>
<td>OV11</td>
<td>250±1.25</td>
<td>0.24±0.63</td>
<td>22±1.29</td>
</tr>
<tr>
<td>OV12</td>
<td>251±1.32</td>
<td>0.27±0.64</td>
<td>22±1.29</td>
</tr>
</tbody>
</table>

* Data are expressed as mean±SD (standard deviation), n=3.

Statistical design

A statistical model incorporating interactive and polynomial terms was used to evaluate the responses.

\[ Y = b_0 + b_1 X_1 + b_2 X_2 + b_1 X_1 + b_2 X_2 + b_1 X_1 X_2 + b_1 b_2 X_1 X_2 \]

Y is the measured response associated with each factor-level combination, \( b_0 \) is the arithmetic mean response of the total 12 runs, \( X_1 \) and \( X_2 \) are the factors studied, \( b_1 \) is the regression coefficient for factor \( X_1 \), computed from the observed response \( Y \). The main effects \((X_1, X_2)\) represent the average result of changing one factor at a time from its low to high value. The interaction terms \((X_1 X_2)\) show how the response changes when two factors are simultaneously changed. The polynomial terms \((X_1^2 \text{ and } X_2^2)\) are included to investigate nonlinearity. Two conclusions could be drawn from the equation: (1) a coefficient with a negative sign increases the response when the factor level is decreased from a higher level to a lower level, and (2) the factor with a higher absolute value of the coefficient and a lower significance value \( P \) has a major effect on the response variables.

A statistical model incorporating interactive and polynomial terms was used to evaluate the responses. The dependent variables, Disintegration time and Hardness showed a wide variation (11 s to 35 s and 1.2 to 4.9 kg/cm² respectively). The data clearly indicates that the response variables are strongly dependent on the selected independent variables. The high values of the correlation coefficient for disintegration time and the hardness indicate a close fit.

The fitted equations (full and reduced) relating the responses to the transformed factor are shown in (Table 7). Analysis of variance (ANOVA) was carried out to identify the insignificant factors, which were then removed from the full model to generate the reduced model (Table 5) and (Table 6).

Table 5: It shows ANOVA for response surface reduced cubic model for disintegration time

<table>
<thead>
<tr>
<th>Response model</th>
<th>Sum of square</th>
<th>df</th>
<th>Mean square</th>
<th>F value</th>
<th>P value</th>
<th>R²</th>
<th>Adequate precision</th>
</tr>
</thead>
<tbody>
<tr>
<td>DT</td>
<td>892.75</td>
<td>6</td>
<td>148.79</td>
<td>343.37</td>
<td>&lt;0.0001</td>
<td>9976</td>
<td>52.708</td>
</tr>
</tbody>
</table>

The Model F-value of 343.37 implies the model is significant. There is only a 0.01% chance that a "Model F-Value" this large could occur due to noise. "Adeq Precision" measures the signal to noise ratio. A ratio greater than 4 is desirable. The ratio of 52.708 indicates an adequate signal. This model can be used to navigate the design space.

Table 6: It shows ANOVA for response surface reduced quadratic model for hardness

<table>
<thead>
<tr>
<th>Response model</th>
<th>Sum of square</th>
<th>df</th>
<th>Mean square</th>
<th>F value</th>
<th>P value</th>
<th>R²</th>
<th>Adequate precision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hardness</td>
<td>16.16</td>
<td>4</td>
<td>4.04</td>
<td>1885.53</td>
<td>&lt;0.0001</td>
<td>0.9991</td>
<td>126.057</td>
</tr>
</tbody>
</table>

The Model F-value of 1885.53 implies the model is significant. There is only a 0.01% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob > F" less than 0.0500 indicate model terms are significant. "Adeq Precision" measures the signal to noise ratio. A ratio greater than 4 is desirable. The ratio of 126.057 indicates an adequate signal. This model can be used to navigate the design space.

Table 7: It shows summary of result of regression analysis

<table>
<thead>
<tr>
<th>Model*</th>
<th>( b_0 )</th>
<th>( b_1 )</th>
<th>( b_2 )</th>
<th>( b_{12} )</th>
<th>( b_{12}^2 )</th>
<th>( b_{12}^2 )</th>
<th>( b_{12}^2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>FM</td>
<td>22.58</td>
<td>-6.50</td>
<td>-11.50</td>
<td>-0.25</td>
<td>-0.75</td>
<td>-0.25</td>
<td>-0.25</td>
</tr>
<tr>
<td>RM</td>
<td>22.58</td>
<td>-6.50</td>
<td>-11.50</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Model*</td>
<td>( b_0 )</td>
<td>( b_1 )</td>
<td>( b_2 )</td>
<td>( b_{12} )</td>
<td>( b_{12}^2 )</td>
<td>( b_{12}^2 )</td>
<td>( b_{12}^2 )</td>
</tr>
<tr>
<td>FM</td>
<td>3.02</td>
<td>0.27</td>
<td>-1.62</td>
<td>-0.10</td>
<td>-</td>
<td>-0.67</td>
<td>-</td>
</tr>
</tbody>
</table>

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For disintegration time, the coefficients of $X_1$ and $X_2$ that is, $b_1$, and $b_2$ respectively, bear a negative sign, thus on increasing the concentration of Mannitol and concentration of camphor, a decrease in disintegration time is observed. For hardness, the coefficients of $X_1$ and $X_2$ that is, $b_1$, and $b_2$ respectively, bear a positive sign and negative sign respectively, thus on increasing the concentration of mannitol and concentration of camphor, an increase and decrease in hardness is observed. When a higher percentage of camphor is used, porosity in the tablet matrix is greater and thus assists in water uptake and subsequent disintegration. Further result showed that mannitol concentration had significant effect on tablet hardness, thus by using combination of mannitol and camphor provide tablets with high mechanical strength with low disintegration time.

Validation of statistical model

To validate the statistical model checkpoint batches, CP1 and CP2 were prepared according to the formula (Table 8). From the response surface plot (Fig. 2 and Fig. 3) and the calculations from the statistical equation obtained by regression, the results revealed the close match of the experimental results. Thus, we can conclude that the statistical model is mathematically valid. The best batch was selected after considering the requirements of an FDT. To fulfill these requirements, concentration of mannitol was set maximum and concentration of camphor 15%. Disintegration time and hardness were kept in range. The batches’ dissolution rates were also considered and batches with higher dissolution rates were given priority. Different constraints were applied; solution with desirability 1 was selected (Table 9).

Table 8: It shows comparison of predicted values and experimental values for check point batches

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Predicted Values (DT)</th>
<th>Experimental Values (DT)</th>
<th>Residual (Predicted)</th>
<th>Experimental Values (Hardness)</th>
<th>Residual (Experimental)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CP1</td>
<td>15.81</td>
<td>17±1.24</td>
<td>1.1</td>
<td>2±0.89</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>$X_1 = +1$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$X_2 = +0.75$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CP2</td>
<td>9.76</td>
<td>11±1.17</td>
<td>1.24</td>
<td>1.6±0.95</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>$X_1 = +0.75$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$X_2 = +1$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Data are expressed as mean±SD (standard deviation), n=3.

Fig. 1: It shows in-vitro release profile of optimized formulation (OFDT) and marketed product (ONDEM MD 8)

Fig. 2: It shows response surface plot eliciting the effect of $X_1$ (mannitol concentration) and $X_2$ (camphor concentration) on $Y_1$ (DT)
Fig. 3: It shows response surface plot eliciting the effect of $X_1$ (mannitol concentration) and $X_2$ (camphor concentration) on $Y_2$ (hardness)

Table 9: It shows predicted desirability:

<table>
<thead>
<tr>
<th>Number</th>
<th>Mannitol</th>
<th>Camphor</th>
<th>Hardness</th>
<th>DT</th>
<th>Desirability</th>
<th>Selected</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50</td>
<td>15</td>
<td>4.125</td>
<td>32.083</td>
<td>1.000</td>
<td></td>
</tr>
</tbody>
</table>

Predicted response at 95% confidence (n=1)
- Response: Hardness
  - Prediction: 4.125
  - Std Dev: 0.046291
  - SE (n=1): 0.054281
  - 95% PI low: 3.9964
  - 95% PI high: 4.2533
- Response: DT
  - Prediction: 32.0833
  - Std Dev: 0.658281
  - SE (n=1): 0.841161
  - 95% PI low: 29.9211
  - 95% PI high: 34.2456

Friability of optimized tablet was below 1% which showed good mechanical resistance. All the parameters i.e. thickness, diameter, weight, friability, drug content and wetting time were under acceptable limits.

Table 10: It shows characterization of optimized tablet (OFDT)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Thickness</th>
<th>Diameter</th>
<th>Weight</th>
<th>Friability</th>
<th>Drug Content</th>
<th>Wetting time</th>
</tr>
</thead>
<tbody>
<tr>
<td>OFDT</td>
<td>3.9±0.72</td>
<td>9.0±0.24</td>
<td>250±1.38</td>
<td>0.36±0.89</td>
<td>99.57±1.18</td>
<td>23±0.68</td>
</tr>
</tbody>
</table>

*Data are expressed as mean±SD (standard deviation), n=3.

(Fig. 4) shows a micrograph of the cross section of a high porosity fast dissolving tablet. It was found that many porous cavities in the tablet were formed due to the sublimation of camphor.

Comparison of predicted responses and observed values for the disintegration time and hardness were in close agreement (Table 11), and the models were found to be valid. Thus, full factorial design with two factors can be successfully used to optimize the formulations.

Table 11: It shows comparison between predicted and observed response

<table>
<thead>
<tr>
<th>Predicted Values * (Disintegration time)</th>
<th>Experimental Values * (Disintegration time)</th>
<th>Predicted Values * (Hardness)</th>
<th>Experimental Values * (Hardness)</th>
</tr>
</thead>
<tbody>
<tr>
<td>32.0833±0.65</td>
<td>31±0.81</td>
<td>4.125±0.046</td>
<td>4.0±1.025</td>
</tr>
</tbody>
</table>

*Data are expressed as mean±SD (standard deviation), n=3.
CONCLUSION

Response surface methodology was used to generate a highly significant mathematical model. A statistical experimental design allowed collecting maximum information with minimum number of experiments. In the present investigation Fast dissolving tablets of Ondansetron HCl having rapid disintegration and good mechanical strength was prepared using sublimation technique. Result of the study showed that disintegration time and hardness was strongly dependent on concentration of mannitol and camphor. Comparison of predicted responses and observed values for the same showed close agreement, and the models were found to be valid. Hence, 3 level full factorial design and statistical models can be successfully used to optimize the formulations.

REFERENCE