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ARTICLE ON FAST DISSOLVING TABLETS: EFFECTIVE THERAPEUTIC ACTION

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ABSTRACT

The demand for fast dissolving tablet (FDT) has been growing during the last decade especially for elderly and children who have swallowing difficulties. The fast dissolving tablets of Prochlorperazine Maleate were prepared by using different technique like direct compression, sublimation, solid dispersion and complexation methods. The prepared tablets were evaluated for various parameters like weight variation, hardness, friability, disintegration time and drug content, water absorption ratio, wetting time, in-vitro drug release, FTIR, DSC studies and short term stability studies. The tablets prepared by direct compression method possess. IR spectral analysis and DSC study showed that there was no drug interaction with formulation additives of the tablet, short term stability studies on the formulations indicated that there are no significant change in hardness, friability, drug content and in-vitro drug release ($p < 0.05$). IR spectral analysis the pure drug characteristic absorption bands of formulations absorption bands have shown all most same range. As there is no variation and shift in the position of characteristic absorption bands it can be justified there is no interaction between drug and polymer. The DSC study during the formulation chemical reaction has not taken place to result into a single product.

Key words: Fast dissolving tablet, Prochlorperazine Maleate, croscarmellose sodium, sodium starch glycolate, crospovidone, Kyron T-314, Disintegration time.

1. INTRODUCTION

1.1 FAST DISSOLVING TABLET

Fast dissolving oral films are most advanced form of solid dosage form due to more flexibility and comfort. It improves the efficacy of API dissolving within minute in oral cavity after the contact with less saliva as compared to fast dissolving tablet without chewing and no need of water for administration 1. It gives quick absorption and instant bioavailability of drug due to high blood flow and permeability of oral mucosa which is 4-1000 times greater than that of skin.

Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passed into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form. Fast dissolving oral films are useful in patients such as pediatric, geriatric, bedridden, emetic

patients, diarrhea, sudden episode of allergic attacks, or coughing for those who have an active life style. It is also useful whether local action desired such as local anesthetic for toothaches, oral ulcers, cold sores or teething 2.

Fast dissolving drug delivery has become a novel and widely accepted dosage form by consumers and gaining the interest of large number of pharmaceutical industries, due to several advantages. This fast dissolving drug delivery system is suited for the drugs which undergo high first pass metabolism and is used for improving bioavailability with reducing dosing frequency to mouth plasma peak levels, which in turn minimize adverse/side effects and also make it cost effective. OFDFs are very similar to postage stamp in their shape, size and thickness that dissolves or disintegrates quickly in the oral cavity resulting in solution or suspension for rapid absorption. Fast Dissolve technologies can be divided in to three broad groupsLyophilized systems,compressed tablet based systemsandThin Film strips 3, 4,

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 solid dosage forms are tablet and capsule. One drawback of these dosage forms however is the difficulty to swallow. Dysphasia or difficulty in swallowing is seen nearly 35% in the general population. This disorder is also associated with number of medical conditions including stroke, Parkinson's disease, AIDS, head and neck radiation therapy and other neurological disorders including cerebral palsy.1-3

Many elderly persons will have difficulties in taking conventional solid dosage form (tablets and capsules) because of their hand tremors and dysphasia. Swallowing problems are also common in young individuals because of their under developed muscular system. Other groups, who may experience problems in swallowing solid dosage form, are the mentally ill, the developmentally disabled, uncooperative patients andreduced 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 of tablets may become difficult.4

To fulfill these medical needs, the pharmaceutical technologist have devoted considerable effort to develop a novel type of dosage form for oral administration, the Fast Dissolving Tablet (FDT), tablet that disintegrates and dissolves rapidly in saliva without need of water. The fast dissolving tablets usually dissolve in oral cavity within 15 to 60 s. The faster the drug goes into solution, the quicker the absorption and onset of clinical effects. The development of fast dissolving tablets also provides line extension in the market place.1-4

Nausea is an unpleasant sensory and emotional experience accompanied by an autonomic driven physiological change of paller and upper GI track hyper secretion [1]. Current oral formulation of aprepitant are indicated for administration of multiple doses, which was due to the half-life of approximately 9-13 h with a time to peak plasmas level of 4 h [2].

Approximately 40% of patients who receive chemotherapy have experienced with nausea and vomiting [3, 4]. Control of nausea and vomiting following chemotherapy and surgery has been improved in recent years due to the advancement of novel, effective, and better-tolerated antiemetic therapies [5-7]. Conventional oral drug delivery systems, including solutions, suspension, tablets and capsules are difficult to administer to patients with dysphagia. Swallowing problems can also be appear often in specific populations, including pediatric, elderly, nauseated patients and developmentally disabled patients. In addition to these difficulties convenience is also a notable concern associated with oral antiemetics like the patients taking tablet formulations require water to ease swallowing, which is not always available [8, 9]. Also, crushing tablets or removing contents from capsules may change the absorption of a drug. In addition to change in nontraditional drug delivery systems, oral delivery formulations have continued to develop to enhance the dissolution and absorption. Fast dissolving tablets (FDTs) have been designed to allow a solid dose to be rapidly dissolved in the oral cavity without the need for water [10-12].

Several approaches have been used to formulate FDTs like freeze-drying, tablet molding, sublimation, direct compression, spray drying etc. Out of theses direct compression and lyophilization have become the most popular used techniques. The tablets prepared by lyophilization technique have very porous structures and hence allow fast disintegration of the tablets. However, high porosity leads to poor physical resistance, in addition to its cost-intensive production process. On the other hand the tablets produced by direct compression method can be hard and attain low friability. This method requires efficient disintegrants to enhance the breaking up of the tablets [12-14].

Hence, based on the rationale of the proposed research work, the aim of the present study was to develop and formulate fast dissolving tablet of aprepitant by direct compression method for the direct absorption of drug via transmucosal lining to the systemic circulation. The proposed formulation has the potential to improve disintegration time and possess sufficient mechanical strength to produce rapid onset of action and patient compliance.

Material and method:

Prochloperazine Maleate was obtained from Mehta Pharmaceuticals, Mumbai, Promethazine Theoclate from Mehta Pharmaceuticals, Mumbai. Cisplatin IV Injection from Pfizer (Perth) Pvt Ltd., Australia. Croscamellose Sodium from Signet Chemicals, Mumbai. Crospovidone also from Signet Chemicals, Mumbai. Sodium Starch Glycolate also from Signet Chemicals, Mumbai. Sodium Bi Carbonate from Central Effervescent Drug House (P) Ltd., Mumbai. Citric Acid from Central Drug House (P) Ltd., Mumbai. Menthol from Central Drug House (P) Ltd., Mumbai. Camphor from Central Drug House (P) Ltd., Mumbai. Thymol from Central Drug House (P) Ltd., Mumbai. Solubility B-Cyclodextrin Signet Chemicals, Mumbai. Enhancers PEG-4000 Central Drug House (P) Ltd., Mumbai. Microcrystalline Cellulose (Avecil)
Signet Chemicals, Mumbai. Sucrose Central Drug House (P) Ltd., Mumbai. Lactose Central Drug House (P) Ltd., Mumbai. Mannitol Central Drug House (P) Ltd., Mumbai
Lubricant Magnesium Stereate Central Drug House (P) Ltd., Mumbai. Glidant Talc Central Drug House (P) Ltd., Mumbai. Dibasic Sodium Phosphate E.Merck (India) Ltd., Mumbai
Monobasic Sodium Phosphate from E.Merck (India) Ltd., Mumbai.
Sodium Hydroxide E.Merck (India) Ltd., Mumbai. Methanol S.D. Fine Chem. Ltd., Mumbai
Acetone S.D. Fine Chem. Ltd., Mumbai.

Result And Discussion:

WETTING TIME

Wetting time of the tablets was measured using a piece of tissue paper (12 cmx10.75 cm) folded twice, placed in a small petridish (ID = 6.5 cm) containing 6 ml ofSorenson's buffer (pH 6.8). A tablet was put on the paper, and the time for thecomplete wetting was measured.35, 45-47

Fig. 1: *In vitro* wetting property

In Vitro Dispersion Time

In vitro dispersion time was measured by dropping a tablet in a glass cylinder containing 6 ml of Sorenson's buffer (pH 6.8). Six tablets from each formulation were randomly selected and *in vitro* dispersion time was performed.46, 48, 49

Fig. 2: *In vitro* dispersion property

TECHNOLOGY FOLLOWED – SUPERDISINTEGRANT ADDITION

The superdisintegrants (Ac-di-sol, sodium starch glycolate and crospovidone) in varying concentration (1-5% w/w) are used to develop the tablets. All the ingredients were passed through sieve no. 60 and were cogrounded in a glass pestle motor.25-27

1 TABLE: FORMULATION OF DRUG FREE TABLETS WITH SUPERDISINTEGRANTS

Ingredients (mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**	**F13**	**F14**	**F15**
Ac-di-sol	**1**	**2**	**3**	**4**	**5**	-	-	-	-	-	-	-	-	-	-
Sodium starch glycollate	-	-	-	-	-	**1**	**2**	**3**	**4**	**5**	-	-	-	-	-
Crospovidone	-	-	-	-	-	-	-	-	-	-	**1**	**2**	**3**	**4**	**5**
Avicel PH102	**55**	**54**	**53**	**52**	**51**	**55**	**54**	**53**	**52**	**51**	**55**	**54**	**53**	**52**	**51**
Lactopress	**25**	**25**	**25**	**25**	**25**	**25**	**25**	**25**	**25**	**25**	**25**	**25**	**25**	**25**	**25**
Mannitol	**15**	**15**	**15**	**15**	**15**	**15**	**15**	**15**	**15**	**15**	**15**	**15**	**15**	**15**	**15**
Talc	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**
Magnesium stearate	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**

Technology Followed - Sublimation

Another technology employed for developing fast dissolving tablets were incorporating subliming agents (camphor, thymol and menthol) in varying concentration (5-20% w/w). Ingredients shown in Table 4.2 were co-grounded in glass pestle glass mortar. The mixed blends of excipients were compressed using a single punch machine to produce flat faced tablets weighing 100 mg. Tablets were subjected for drying for 6 h under vacuum (30 kpa) at 50o for sublimation to make tablets porous.28-30

2. TABLE: FORMULATION OF DRUG FREE TABLETS WITH SUBLIMATING AGENTS

Ingredients (mg)	**F16**	**F17**	**F18**	**F19**	**F20**	**F21**	**F22**	**F23**	**F24**	**F25**	**F26**	**F27**
Camphor	**5**	**10**	**15**	**20**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Thymol	**-**	**-**	**-**	**-**	**5**	**10**	**15**	**20**	**-**	**-**	**-**	**-**
Menthol	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**5**	**10**	**15**	**20**
Avicel PH102	**51**	**46**	**41**	**36**	**51**	**46**	**41**	**36**	**51**	**46**	**41**	**36**
Lactopress	**25**	**25**	**25**	**25**	**25**	**25**	**25**	**25**	**25**	**25**	**25**	**25**
Mannitol	**15**	**15**	**15**	**15**	**15**	**15**	**15**	**15**	**15**	**15**	**15**	**15**
Talc	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**
Magnesium Stearate	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**

Technology Followed - Effervescent

Fast dissolving tablets were prepared by using citric acid and sodium-bicarbonate in combination in (1:2 ratio) with other excipients shown in Table 4.3 was co-grounded in glass pestle glass mortar. These tablets contain (1-5% w/w) effervescent agent.31-33

2. TABLE: Effervescent study of drug

Ingredient (mg)	**F28**	**F29**	**F30**	**F31**	**F32**
Citric Acid	0.33	0.66	1.00	1.32	1.65
NaHCO3	0.67	1.34	2.00	2.68	3.35
Avicel PH 102	55	54	53	52	51
Lactopress	25	25	25	25	25
Mannitol	15	15	15	15	15
Talc	2	2	2	2	2
Magnesium stearate	2	2	2	2	2

ANALYTICAL TECHNIQUES AND PREFORMULATIONSTUDIES

DRUG ANALYSIS

Melting Point: The melting point of the prochlorperazine maleate was determined bycapillary fusion method. A capillary was sealed at one end filled with a small amountof prochlorperazine maleate and the capillary was kept inverted i.e. sealed enddownwards into the melting point apparatus.13

Reported Melting Point: 229o Observed Melting Point: 230o

***Infrared Spectral Assignment*:** The FTIR analysis of the sample was carried out forqualitative compound identification. The pellet of approximately 01 mm diameter ofthe prochlorperazine maleate was prepared grinding 3-5 mg of sample with 100-150mg of potassium bromide in pressure compression machine. The sample pellet wasmounted in FTIR (8400S, Shimadzu) compartment and scanned at wavelength 4000– 500 cm-1. On analysis of the FTIR spectra of the reference spectra (Fig.1) givenin Clarke Analysis and pure prochlorperazine maleate (Fig.2), no major differenceswere observed in the characteristic absorption peak (751, 1220, 1280, 1569 cm−1)

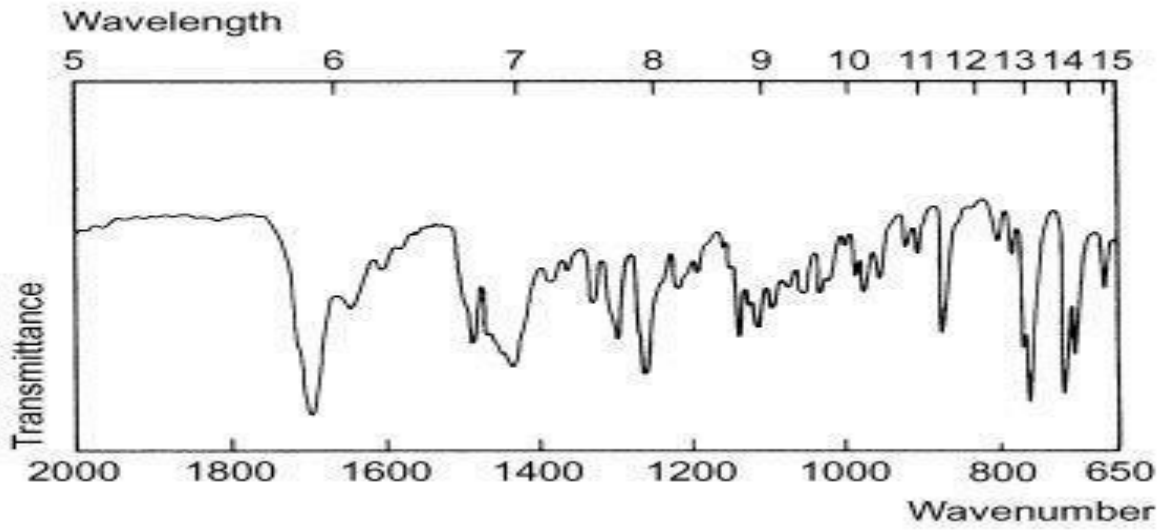

FIG.3: FTIR SPECTRA OF PROCHLORPERAZINE MALEATE GIVEN IN CLARKE'SANALYSIS

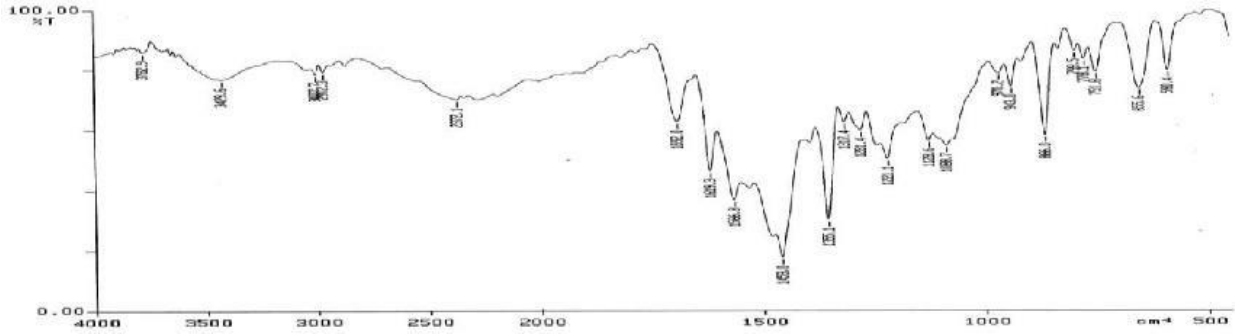

Fig.4: FTIR Spectra of prochlorperazine maleate determined experimentally

***Solubility*:** The solubility of prochlorperazine maleate was determined in differentsolvent systems. Small amounts of the prochlorperazine maleate was added to 5 ml ofeach solvent in screw capped glass tubes and shaken. The solutions were examinedphysically for the absence or presence of prochlorperazine maleate particles.

Qualitative solubility determined by UV- Spectrophotometer at 254 nm.

TABLE 4: SOLUBILITY PROFILE OF PROCHLORPERAZINE MALEATE

Solvent	Solubility	Solubility (gm/ml)
Distill Water	+	0.002±0.01
0.1N Hydro Chloride	++	0.041±0.016
0.1N Sodium Hydroxide	++	0.057±0.029
Ethanol	+++	0.231±0.028
Ether	++	0.049±0.031
Chloroform	++	0.062±0.023
Buffer (pH 6.8)	++	0.055±0.011
Acetone	-	-

Freely soluble +++ Soluble ++ Slightly soluble + Practically insoluble -

Ultraviolet Absorption Maxima*:*

Preparation of Sorenson's Buffer (pH 6.8)

24.5 ml of 0.2 M dibasic sodium phosphate and 0.2 M 25.5 ml of monobasic sodiumphosphate was placed in 100 ml volumetric flask, and make up the volume 100 ml bywater. UV spectra absorption in the rage 200 to 400 nm of a 50 □g/ml solution in Sorenson's buffer (pH 6.8) was measured

The absorption maxima (λmax)of prochlorperazine maleate (50 µg/ml) in thesolution was found to be 254 nm and 305 nm which was concordant with the ClarkeAnalysis shown in Table 4.4 and Fig.3.

TABLE 5: DETERMINATION OF WAVELENGTH MAXIMA (ΛMAX)

Wavelength	Absorbance
200	0.612
224	0.337
254	0.682
274	0.035
305	0.084
361	0.003

Prochlorperazine maleate (100 mg) was dissolved in small amount ofSorenson's buffer (pH 6.8) in a 100 ml of volumetric flask and final volume wasmade with the Sorenson's buffer. 10 ml of this solution was diluted to 100 ml withSorenson's buffer (pH 6.8) in a 100 ml volumetric flask to obtain a stock solution of100 µg/ml. **A**liquots of 1, 2, 3, 4, 5, 6 and 7 ml were taken from stock solution in 10ml volumetric flasks and volume was made up to 10 ml with buffer (pH 6.8). Theabsorbance of these solutions was measured at 254 nm. The calibration curve wasplotted between concentration and absorbance.

TABLE 6: CALIBRATION CURVE OF PROCHLORPERAZINE MALEATE

Concentration (µg/ml)	Absorbance (254 nm)
0	0
10	0.155
20	0.294
30	0.423
40	0.551
50	0.674
60	0.815

70	0.941

Conclusion:

Fast dissolving tablets are innovative dosage forms developed and specially designed to overcome some of the problems that seen in conventional solid dosage form i.e. difficulty in swallowing of the tablet in geriatric and pediatric patients. Fast dissolving tablets are designed to dissolve or disintegrate quickly in the saliva generally within less than 60 seconds (range of 5-60 seconds). Fast dissolving tablets have better patient compliance and acceptance may improve biopharmaceutical properties, bioavailability improved efficacy, convenience, and better safety compared with conventional oral dosage forms. The popularity of FDTs has increased fabulously over the last decade. FDTs need to be formulated for psychotic patients, bedridden, geriatric, pediatric patients, for those patients who may not have access to water, patients who are busy in traveling. FDTs formulations formulated by some of these convetional and patent technologies and FDTs have sufficient mechanical strength, quick disintegration/dissolution in the buccal cavity without water. The newer technologies utilized for the formulation of the FDTs that provide more effective dosage forms with more advantages and minimal disadvantages.

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