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FORMULATION AND *IN VITRO* COMPARATIVE EVALUATION OF ORODISPERSIBLE TABLETS OF ESOMEPRAZOLE

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ABSTRACT

In the present work, an attempt has been made to formulate oral dispersible tablets of Esomeprazole by three different methods. Conventional tabletting procedure was followed for the preparation of tablets. Nine batches of tablets were prepared and evaluated for general appearance and physical parameters, drug content, *in vitro* disintegration, *in vitro* dispersion, *in vitro* drug release, kinetic and stability studies. Formulations prepared by superdisintegrants addition method emerged as the best formulations, as they showed rapid *in vitro* disintegration time, *in vitro* dispersion time and drug release at the end of 5 min, apart from taste and excellent mouth feel compared to formulations prepared by sublimation and effervescent methods. It was concluded that oral dispersible tablets of Esomeprazole can be successfully formulated and will be used as a novel drug dosage form for pediatrics and geriatrics with improved patient compliance.

KEYWORDS: Esomeprazole; Orodispersible tablets; Superdisintegrants, Sublimation.6.

INTRODUCTION

Recent developments in technology have presented viable dosage alternatives for patients who have difficulty in swallowing the tablets or liquids. Traditional tablets and capsules administered with an 8-oz. glass of water may be inconvenient or impractical for some patients. Dysphagia or chewing solid dosage forms, which is a common problem of all age groups, particularly pediatrics and geriatrics, because of physiological changes associated

with these groups (Aurora J & Pathak V., 2005). Dysphagia is also associated with the number of medical conditions, including stroke, Parkinsons disease, AIDS, head and neck radiation therapy and other neurological disorders, including cerebral palsy. Other categories that experience problems using conventional oral dosage forms include are mentally ill, uncooperative and nauseated patients, those with motion sickness, sudden episodes of allergic attack or coughing (Bogner RH & Wilkosz MF., 2005), sometimes, it may be difficult to swallow the conventional products due to unavailability of water (Kaushik D *et al.*, 2004). These problems cause the need for delivering drugs to patients efficiently, and with few side effects have prompted pharmaceutical companies to engage in the development of new drug delivery systems. Oral dispersible tablets (ODT) are perfect fit for all this kind of patients. ODT is those solid dosage forms when put on the tongue, disintegrate or dissolve instantaneously, releasing the drug, within a few seconds without the need of water. When this type of tablet is placed into the mouth, the saliva will serve to rapidly disintegrate the tablet. The faster the drug into solution, quicker the absorption and onset of clinical effect. ODT release drug in the mouth for absorption through local oral mucosal tissues and through pregastric (i.e., oral cavity, pharynx and oesophagus), gastric (i.e., stomach) and post gastric (i.e., small and large intestine) (Pfister WR &, Ghosh TK., 2005) In such cases, the bioavailability of some drugs may be increased due to absorption of drugs in oral cavity and also due to pregastric absorption of saliva containing dispersed drugs that pass down significantly greater than those observed from conventional dosage forms (Panigrahi D *et al.*, 2005). ODT are also known as fast dissolving, mouth dissolving, rapid-dissolve, quick disintegrating, orally disintegrating, rapimelt, fastelts, melt-in-mouth, quick dissolving, porous tablets, EFVDAS, or Effervescent Drug Absorption System (Sreenivas SA *et al.*, 2005). ODT technology has been approved by United States Pharmacopoeia (USP), Centre for Drug Evaluation and Research (CDER). US- FDA defined ODT as A solid dosage form containing medicinal substances, which disintegrates rapidly, usu- ally within a matter of seconds, when placed upon the tongue. Recently, European Pharmacopoeia also adopted the term Oro Dispersible Tablet (Guidance for Industry).

Cancer chemotherapy causes a lot of adverse effects, of which nausea and vomiting are prime one. This can be clearly seen with model anticancer drug cisplatin, which is first line drug in many types of cancers. Hence anti ulcer drugs like omeprazole, Esomeprazole are administered one hour prior to the administration of anticancer drug (Thomson

Micromedex Healthcare., 2005). However, this becomes a major patient non compliance in the case of children, elderly and bed ridden patients for whom swallowing tablets causes inconvenience (Shu T *et al.*, 2002). Among the dosage forms developed to facilitate ease of medication. The rapid disintegrating tablet (RDT) is one of the most widely employed commercial products (Koizumi K *et al.*, 1997). Hence, present investigation is an attempt to improve patient compliance by formulating antiulcer drug omeprazole in the form of oral dispersible tablets.

MATERIALS AND METHODS

Materials

Esomeprazole was obtained as a gift sample from Ranbaxy Pharmaceuticals, Hyderabad. Croscarmelose sodium, Crospovidone, Sodium bicarbonate, Citric acid, Ammonium bicarbonates were procured from Ozone international, Mumbai. All other chemicals used were of analytical grade.

Table 1: Formulations of oro dispersible tablets

Ingredients (mg/tab	Formulation Code								
	ESD1	ESD2	ESD3	EEV1	EEV2	EEV3	ESL1	ESL2	ESL3
Esomeprazole	20	20	20	20	20	20	20	20	20
Croscarmelose sodium	-	-	-	-	-	-	-	-	-
Crospovidone	8 (4%)	16 (8%) (4%)	24 (12%)	-	-	-	-	-	-
Sodium starch glycolate	-	-	-	-	-	-	-	-	-
Avicel pH102	130	130	130	50	50	50	-	-	-
Mannitol (15%)	30	30	30	129.75	129.75	129.75	100	10	10
Sodium Bicarbonate	-	-	-	-	20 (8%)	25 (10%)	-	-	-
Citric acid (Anhydrous)	-	-	-	20 (8%)	15 (6%)	25 (10%)	-	-	-
Ammonium Bicarbo-nate	-	-	-	-	-	-	150 (60%)	100 (40%)	50 (20%)
Aerosil (2%)	4	4	4	-	-	-	-	-	-
Starch (4%)	-	-	-	8	8	8	8	8	8
Sodium saccharin (1%)	-	-	-	2	2	2	2	2	2
Purified Talc (2%)	4	4	4	4	4	4	4	4	4
Magnesium stearate (1%)	2	2	2	2	2	2	2	2	2
Strawberry flavor (1.5%)	3	3	3	3	3	3	3	3	3

Table 2: Evaluation of orodispersible tablets

Formulation code	Hardness* ± SD (kg/cm^2)	Disintegration Time (sec) ± SD	Dispersion Time (sec) ± SD	Wetting Time(sec)± SD
ESD1	2.5 ± 0.14	18.32 ± 0.67	21.50 ± 1.5	22.14± 2.50
ESD2	2.87 ± 0.22	22.12 ± 2.16	26.00 ± 2.0	25.00 ± 3.28
ESD3	3.22 ± 0.12	16.82 ± 1.16	18.00 ± 1.0	32.00 ± 3.00
EEV1	3.20 ± 0.15	44.80 ± 2.85	47.5 ± 2.94	50.16 ± 2.33
EEV2	2.89 ± 0.14	41.26 ± 2.73	46.31 ±3.51	52.00 ± 3.00
EEV3	3.15 ± 0.25	36.00 ± 3.0	42.64 ± 2.44	42.00 ± 1.89
ESL1	2.4 ± 0.07	26.00 ± 2.0	30.06 ± 2.41	34.16 ± 2.73
ESL2	2.54± 0.08	31.51 ± 1.35	34.12 ± 3.21	36.83 ± 3.21
ESL3	2.70 ± 0.21	33.32 ± 2.5	38.24 ± 3.18	40.00 ± 1.68

Methods

Formulation of orodispersible Tablets

In the present study, orodispersible tablets of Esomeprazole were prepared by direct compression technique.

Preparation of ODT of Omeprazole using Superdi- sintegrant addition Method

The superdisintegrants used were croscarmelose so- dium, crospovidone and sodium starch glycol ate. All the ingredients were passed through a sieve #40 and kept in a hot air oven at 80˚C to make anhydrous and accurately weighed. The drug, superdisintegrants, Avicel pH 102, mannitol sweetener, aerosol, and flavor were triturated well in a mortar to mix them properly. Magnesium stearate and talc were then passed through a sieve #80, mixed and blended with the initial mixture. The mixed blend of drug and excipients was compressed using rotary punch MINIPRESS II (Karnava- thi) tabletting machine to produce tablet weighing 200 mg having a diameter of 8 mm. Following above procedure, three batches of ODT of Esomeprazole in a different ratio were prepared (S. Banker, and G. R. An- derson., 1987).

Preparation of ODT of Esomeprazole by Effervescent Formulation Approach

Sodium bicarbonate and citric acid (anhydrous) were used as effervescent agents. All the ingredients were passed through a sieve #40 and kept in a hot air oven at 80˚C to make anhydrous and accurately weighed. The drug, effervescent agents, Avicel pH 102, mannitol, starch, sweetener, and flavor were triturated well in a mortar to mix them properly. Magnesium stearate and talc were then passed through a sieve #80, mixed and blended with the initial mixture. The mixed blend of drug and excipients was compressed using rotary punch MINIPRESS II (Karnavathi) tabletting machine to produce tablet weighing 200 mg

having a diameter of 8 mm following above procedure, three batches of ODT of Esomeprazole in a different ratio of Sodium bicarbonate and citric acid were prepared.

Preparation of ODT of Esomeprazole by Sublimation Method

Ammonium bicarbonate was used as a sublimable component. Accurately weighed quantities of the drug sublimable component, mannitol and sodium saccharin were mixed and passed through a sieve #40. All the ingredients were grounded in a glass mortar to get a uniform mixture. Then the remaining excipients were added, thoroughly triturated and compressed using the rotary punch MINIPRESS II (Karnavathi) tabletting machine to produce a tablet weighing 200 mg having a diameter of 8 mm. The prepared tablets were packed in an aluminum foil pouch. Following above procedure, three batches of ODT of Esomeprazole, in a different ratio of ammonium bicarbonate were prepared.

Evaluation of oro dispersible Tablets Hardness and Friability

Hardness and Friability of tablets were determined as per IP by using Monsanto hardness tester and Roche Friabilator respectively (British Pharmacopoeia., 1988).

Wetting time

A piece of tissue paper folded twice was placed in a small petridish containing 6 ml of simulated saliva pH (phosphate buffer pH 6.8). A tablet was put on the paper and the time required for complete wetting was measured. Six trials for each batch were performed and an average time for wetting with standard deviation was recorded (Wade A & Weller PT., 1984).

Surface pH

The surface pH of the tablets was determined in order to investigate the possibility of any side effects due to change in pH *in vivo* since an acidic or alkaline pH may cause irritation to the buccal mucosa. A combined glass electrode was used for the purpose. The tablets were allowed to swell by keeping them in contact with 1 ml of simulated saliva for 2 h and pH was noted by bringing the electrode in contact with the surface of the formulations (Wade A & Weller PT, 1984) and allowing it to equilibrate for 1 min.

Drug content estimation

As per USP, twenty tablets were weighed and powdered. A quantity of powder equivalent to 10 mg of omeprazole was accurately weighed, transferred into a 100 ml

volumetric flask and dissolved in 0.1 N HCl. After shaking for 10 min, the volume was made up to 100 ml with 0.1 N HCl. The above solution (1 ml) was taken and diluted to 10 ml and was analyzed spectrophotometrically at 305 nm and percentage of Esomeprazole was determined (Wade A & Weller PT., 1984).

Weight variation test

Uniformity of weight test as described in the IP was followed. Using this procedure weight variation range of all batches of formulations were determined and recorded (Liebermann HA., 1990).

Uniformity of drug content

One tablet was powdered and transferred to a 100 ml volumetric flask and dissolved in 0.1N HCl. The volume was made up to 100 ml. From this 1 ml was pipetted out and diluted to 10 ml with 0.1N HCl in 10 ml volumetrical flask. The absorbance was measured spectrophotometrically at 305 nm. The test was carried out individually for five tablets from each formulation (Wade A & Weller PT., 1984).

***In vitro* Disintegration time**

In vitro disintegration time was determined using a disintegration test apparatus (Thermonik). A tablet was placed in each of the six tubes of the apparatus, one disc was added to each tube. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured in seconds (Wade A & Weller PT., 1984)

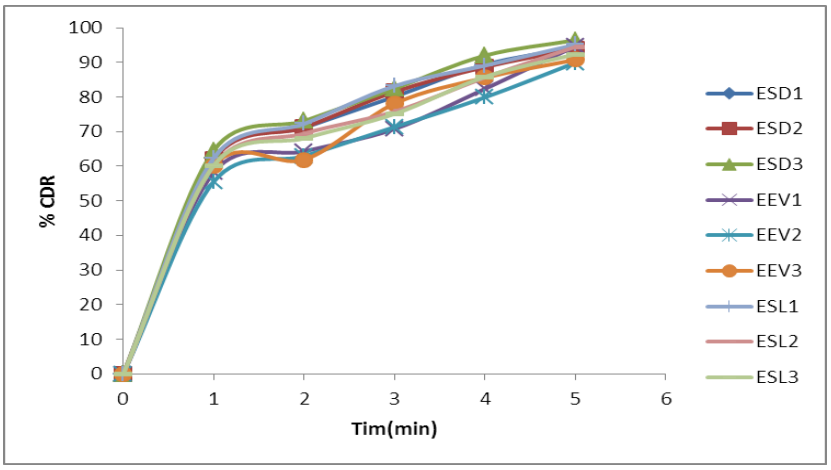

Figure 1: In vitro drug release profile

***In vitro* Dispersion Time**

A tablet was put into a measuring cylinder containing 6 ml of phosphate buffer pH 6.8

(simulated saliva pH). Time required for complete dispersion of a tablet was recorded. This test was performed for six tablets from each batch and average time taken for dispersion with standard deviation was recorded (Kuchekar BS *et al.*, 2003; Ozeki T *et al.*, 2003).

***In vitro* drug release studies**

In vitro drug release studies were carried out by using USP XXIII dissolution apparatus II (Paddle type) [Electro lab (TDT-06T) Tablet Dissolution Tester] at 50 rpm. The drug release profile was studied in 900 ml of hydrochloric acid buffer at pH 1.2 by maintaining at 37 +_ 0.5˚C. Aliquots of 10 ml of a dissolution medium were with- drawn at specific time intervals (1, 2, 3, 4 and 5 min), filtered and the amount of drug released was deter- mined spectrophotometrically at 305 nm.

Stability Studies

Twenty tablets from each batch were selected at ran- doom and were packed in aluminum foil. Ten tablets from each batch were kept in a desiccator at room temperature, and the other 10 were kept at room temperature on a shelf (at RH 80%) for one month. The tablets were checked for physical appearance, hardness, weight difference, *in vitro* dispersion time and *in vitro* drug release profile. Then the results were compared with those obtained immediately after compression.

RESULTS AND DISCUSSION

All the ODT formulations by superdisintegrant addition method showed less *in vitro* disintegration time (< 23 sec) and *in vitro* dispersion time (< 26 sec). The formulation containing croscarmelose sodium (5% w/w) for- mulation PSD3 emerged to be the best. This is because of least hardness of 2.22 ± 0.12 Kg/cm and presence of croscarmelose sodium in higher concentration. Among the superdisintegrant formulations croscarmelose less disintegration & dispersion time because it will draw water & swell. Crospovidone will increase disintegration time. As a result crospovidone will increase the disintegration & dispersion time.

Among the effervescent formulations, PEV1 showed least disintegration time & dispersion time and among the sublimation formulations PSL1 showed least disintegration & dispersion time may be due to presence of sodium bicarbonate & ammonium bicarbonate.

As far as and drug content, weight variation, friability tests are concerned formulation were

within IP limits. The surface pH is concerned all the formulations re- mained within 6.5-7.5 pH. Hence, it was found to be compatible with the oral cavity pH (6.8).

Wetting time of tablets of all formulations reflected in the disintegration time & dispersion time (Table 2) and *in vitro* release profile (Fig 1).

Stability studies indicated that no significant variation was found as far as physical & in process parameters of formulations were concerned. Hence, the formulations were found to be stable and also no shift in λ max was found.

CONCLUSION

The oral dispersible tablets of Esomeprazole were prepared by three different methods and among the methods employed superdisintegrant formulations was found to be better compared to other two methods like effervescent and sublimation formulations. Further, the formulation parameters reflected in the release of drug from the formulations. Hence, the methods employed to prepare the formulations of ODT found to be effective, and the formulations were found.

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