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Formulation and Evaluation of Ora-Solv Tablets of Pantoprazole Sodium

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Abstract

Pantoprazole is a potent and selective proton pump inhibitor. It is an effective agent in the treatment of Peptic ulcers, Gastro-oesophageal reflux disease (GERD), Oesophagitis, Zollinger-Ellison syndrome and other GI hypersecretory disorders. It provides rapid symptoms relief up to 85-90% of Ulcer patients within 1 hour of treatment. It has mediocre bioavailability of 50% and poor aqueous solubility and thus makes its absorption and dissolution rate limited, delaying its onset of action to certain extent. Pantoprazole is available as conventional tablet in the market and many patients find it difficult to swallow these, especially paediatric and geriatric subjects which results in high incidence of non-compliance and ineffective therapy. In this present study, an effort has been made to formulate fast disintegrating and rapid release tablets, also called as Ora-Solv tablets, of Pantoprazole using two different Superdisintegrants viz. Croscarmellose sodium and Sodium starch glycollate (SSG) by direct compression method. Evaluation of the tablets showed that all the tablets were found to be within official limits and the disintegration time for the formulations ranged from 15 s to 25 s. From the overall observations, formulation F_6 containing 15% w/w concentration of SSG was considered to be the optimized formulation which releases up to 100.70% of the drug in 15 minutes. The formulated OST's have potential advantages over conventional marketed tablets with their improved patient compliance, both in geriatrics and paediatrics, ease of administration and bio-availability.

Keywords: Pantoprazole, Ora-Solv tablets, Superdisintegrant, Croscarmellose sodium, Sodium starch glycollate, direct compression.

INTRODUCTION

Recently Fast Dissolving Drug Delivery Systems have started gaining popularity and acceptance as New Drug Delivery Systems. [1] Since the development cost of a new chemical entity is very high, the Pharmaceutical companies are focusing on the development of new drug delivery systems for existing drug with an improved efficacy and bioavailability together with reduced dosing frequency to minimize side effects.

Dysphagia (difficulty in swallowing) is seen to afflict nearly 35% of the general population and is common with all age groups. 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.[2] Swallowing of solid dosage forms like Tablets, Capsules and improper dosing of suspension and emulsion may precipitate patient noncompliance with young individuals because of under developed muscular and nervous systems, psychiatric patients, non-cooperative patients and travellers who have little access to water.[3]

The approach to overcome these problems is by formulating Ora-Solv tablets (OST's). Ora-Solv tablets are those which when placed in the tongue, instantaneously disintegrates and releases the drug that dissolves or disperses rapidly in the saliva without the need of drinking water or chewing. OST's usually dissolve in the oral cavity within 15 seconds to 3 minutes. The faster the drug into solution, quicker the absorption and onset of clinical effect. [4]

When formulated as OST, some drugs are absorbed from the mouth, pharynx and oesophagus as the saliva passes down into the stomach which in turn increases the bioavailability of the drug. This is known as pre gastric absorption. Thus in OST, the amount of drug that is subjected to first pass metabolism is reduced as compared to conventional tablets. OST offers a giant leap forward in drug administration by providing a new and easy way of taking medication.[5] OST's are both very porous and inherently soft moulded matrices or tablets compacted at very low compression forces in order to maximize tablet porosity and minimize oral dissolution / disintegration time.[1]

Ora - Solv tablets are also known as Fast dissolving tablets, Mouth dissolving tablets, Fast disintegrating tablets, orally disintegrating tablets, Rapid disintegrating tablets, Oro dispersible tablets and Quick dissolving tablets.[6]

Pantoprazole is a potent and selective proton pump inhibitor. It is an effective agent in the treatment of Peptic ulcers, Gastro-oesophageal reflux disease (GERD), Oesophagitis, Zollinger-Ellison syndrome and other GI hypersecretory disorders. It has poor bioavailability (~50%) and aqueous solubility, thus it is absorption and dissolution rate limited, delaying its onset of action. Pantoprazole is available as conventional tablet in the market and many patients find it difficult to swallow these, especially paediatric and geriatric subjects which results in high incidence of non-compliance and ineffective therapy.

In this present study, an effort has been made to formulate fast disintegrating and rapid release tablets of Pantoprazole using two different superdisintegrants viz. Croscarmellose sodium (CCS) and Sodium starch glycollate (SSG) by direct compression method. The objective of this study was to enhance the safety and efficacy of the drug molecule, achieve better patient compliance, solve problem of difficulty in swallowing, enhance onset of action and provide a stable dosage form [7].

MATERIALS AND METHODS

Materials

Pantoprazole sodium was a kind gift from Vasudha Pharma Ltd. (Andhra Pradesh, India), Croscarmellose sodium and Sodium starch glycollate were purchased from Signet Chemical Corporation, Mumbai. Aerosil and Mannitol

were from Micro Labs (Hosur). Microcrystalline cellulose, Saccharin sodium was purchased from S.D.Fine Chemicals (Mumbai). Acetonitrile (HPLC Grade) and Water (HPLC Grade) were purchased from Merck (India). All other chemicals and reagents were of analytical grade.

Preformulation Studies

Compatibility Studies

FT-IR spectroscopy can be used to investigate and predict any physicochemical interaction between components in a formulation and therefore it can be applied to the selection of suitable chemically compatible excipients while selecting the ingredients.

Angle of Repose

The angle of repose of granules was determined by the funnel method. The accurately weighed powder blend was taken in a funnel. The blend was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation

$$\tan \theta = h / r$$

where *h* and *r* are the height and radius of the powder cone.

Bulk density, Tapped density and Carr's index [8]

Weighed quantity of powder blend was taken in a graduated cylinder and the bulk volume (V_b) was measured, and weight of the blend (M) was determined. The measuring cylinder containing known mass of powder blend was tapped for a fixed time and the tapped volume (V_t) occupied in the cylinder and the weight of the blend (M) was measured. From that bulk density, tapped density and Carr's index were calculated.

$$\text{Bulk density } (e_b) = \frac{M}{V_b}$$

$$\text{Tapped density } (e_t) = \frac{M}{V_t}$$

$$\text{Carr's index (I)} = \frac{e_b - e_t}{e_t} x100$$

Preparation of ORA-SOLV tablets

ORA-SOLV tablets were prepared by direct compression method. In the formulation, each superdisintegrant was employed in three concentrations (5, 10 and 15%). The composition of OST of Pantoprazole sodium is shown in Table 1. Weighed quantities of Pantoprazole sodium along with appropriate concentrations of superdisintegrant, mannitol, microcrystalline cellulose, saccharin sodium were weighed and mixed in geometric progression in a dry and clean mortar. Then the blend was passed through sieve no. 60. Then magnesium stearate was added and mixed well. The dry blend was compressed into tablets using 8 mm convex faced punches in a 10 Station Rotary Tablet Machine [Cadmach, India].

Evaluation of ORA-SOLV tablets

Thickness and diameter [9]

The thickness and diameter of the tablets were carried out using vernier calipers (Mitutoyo corps, Japan). Five tablets were used for the above tests from each batch and results were expressed in millimeters.

Hardness Test [9,10]

Tablets require a certain amount of strength or hardness and resistance to Friability to with stand mechanical shocks of handling in manufacture, packing and shipping. The hardness of tablet was measured by Monsanto hardness tester, five tablets from each batch were used for hardness studies and results were expressed in Kg/cm^2.

Weight variation Test

Twenty tablets were selected at random, individually weighed in a single pan electronic balance (Sartorius Labs) and the average weight was calculated. The uniformity of weight was determined according to I.P. Specification. As per I.P. not more than two of individual weights would deviate from average weight by more than 7.5% and none deviates by more than twice that percentage.

Friability Test

The friability of the tablet was determined using Roche friabilator. It is expressed in percentage (%). 20 tablets were initially weighed ($W_{initial}$) and transferred in to the Friabilator. The Friabilator was operated at 25 rpm for 4 minutes. The tablets are weighed again (W_{final}). The % Friability (F) was then calculated by

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} x100$$

Wetting Time [8]

Wetting time is closely related to the inner structure of tablets and to the hydrophilicity of the excipients. A linear relationship exists between wetting time and disintegration time. Thus wetting time is an important step for disintegration process to take place.

A piece of tissue paper folded twice was placed in a small petridish (internal diameter = 6.5cm) containing 6ml of water. A tablet was placed on the paper and the time for complete wetting of the tablet was measured in seconds. Three trials for each batch were performed and standard deviation was also determined.

Water Absorption ratio [11]

A piece of tissue paper folded twice was placed in a small petridish (internal diameter = 6.5cm) containing 6ml of water. A tablet was placed on the paper and time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio (R) was determined using following equation

$$R = 100 \times \frac{W_a - W_b}{W_b}$$

$W_a \rightarrow$ weight of tablet after water absorption

$W_b \rightarrow$ weight of tablet before water absorption

Drug Content uniformity test

It was determined at λmax 263nm using HPLC (Model - LC10AT-VP, 7725 I Manual Injection, Shimadzu corporation, Japan).

In- Vitro **Dispersion Time** [12]

In-vitro dispersion time was measured by dropping a tablet in a measuring cylinder containing 6ml of pH 6.8 (simulated saliva fluid). The time for the tablet to completely disintegrate into fine particles was noted. Three

tablets from each batch were randomly selected and *in-vitro* dispersion time was performed.

***In – Vitro* Disintegration Time [12]**

The disintegration time of the tablets was determined as per Indian Pharmacopoeial monograph. The test was carried out using Tablet disintegration apparatus. Six tablets from each batch were placed and one litre of distilled water was used as the disintegration medium. The time required to obtain complete disintegration of all the six tablets was noted.

***In – Vitro* Dissolution Studies [12]**

In-vitro drug release studies for Ora-Solv tablets of Pantoprazole Sodium was studied using Dissolution apparatus II USP XX1 model [Paddle type] for the fabricated batches. 900ml of Phosphate buffer solution [pH 6.8] was used as the dissolution medium. The tablet was placed in the dissolution medium and rotated at a speed of 50 rpm maintained at a temperature of 37 ± 0.5°C.

5ml of sample was withdrawn at periodic intervals 0, 5th, 10th, and 15th minute. 5ml of fresh dissolution medium (maintained at the same temperature) was replaced after each time of withdrawal of samples. The samples were analyzed spectrophotometrically at 287.4 nm for the drug content against the respective buffer blank. The mean percentage of Pantoprazole sodium released at various time intervals was calculated from standard graph and plotted against time.

Comparative *Invitro* drug release studies for the optimized formulation with marketed Pantoprazole sodium tablets

To compare the drug release rates of the optimized Ora-Solv Tablets (Batch F6) with that of the commercially available tablets of Pantoprazole sodium, Pantocid-20 (Sun Pharmaceutical Ind Ltd.) was selected as a choice and dissolution studies were carried out. 5ml sample were withdrawn periodically and studied for the previous mentioned standard analysis by UV spectrophotometric method.

Kinetics of Drug release [13]

The optimized formulation F_6 was subjected to kinetic treatment to assess the order of drug release.

A plot of Logarithm of percentage of drug remaining to be released versus time would be linear if the rate of drug release follows First order kinetics

The linear equation for first order drug release plot is

$$\text{Log } C = \text{Log } C_o - \frac{Kt}{2.303}$$

C = concentration remaining at time‘t’

C_o = original concentration

t = time

k = release rate.

RESULTS AND DISCUSSION

Compatibility Studies

The compatibility between the drug and the superdisintegrant was evaluated using FT-IR peak matching method. There was no appearance or disappearance of peaks in the superdisintegrant-drug mixture, which confirmed the absence of any chemical interaction between the drug and the polymer.

Table 1. Composition of ORA - SOLV Tablets (OST’S) of Pantoprazole Sodium

Formulation Code	Drug (mg)	SSG (mg)	CCS (mg)	MCC (mg)	Mannitol (mg)	Aerosil (mg)	Saccharin sodium (mg)	Magnesium Stearate (mg)
F1	20	-	12.5	195.5	15	3	2	2
F2	20	-	25	183	15	3	2	2
F3	20	-	37.5	170.5	15	3	2	2
F4	20	12.5	-	195.5	15	3	2	2
F5	20	25	-	183	15	3	2	2
F6	20	37.5	-	170.5	15	3	2	2

Table 2. Flow properties of powder blend

S.No	Parameters	F_1	F_2	F_3	F_4	F_5	F_6
1	Bulk density (g/ml)	0.5283	0.4940	0.4556	0.3166	0.3356	0.3602
2	Tapped density(g/ml)	0.5870	0.5489	0.5125	0.3431	0.3636	0.3903
3	Carr’s index (%)	10	10.002	11.102	7.70	7.701	7.712
4	Angle of repose (θ)	25°.25’	27°.89’	28°.09’	20°.56’	23°.04’	24°.28’

Table 3. Evaluation of various parameters

Formulation Code	Friability (%)	WeightVariation(mg) ± S.D	Wetting Time (sec) ± S.D (n=3)	Water Absorption Ratio
F_1	0.445	246.95 ± 0.13	7.50 ± 0.23	30.18
F_2	0.392	254.90 ± 0.98	7.00 ± 0.32	34.07
F_3	0.599	250.10 ± 0.89	7.75 ± 0.27	34.69
F_4	0.392	248.55 ± 0.62	8.00 ± 0.05	33.49
F_5	0.530	235.45 ± 1.08	7.75 ± 0.02	35.88
F_6	0.457	251.60 ± 0.48	7.50 ± 0.03	31.55

Flow properties

The angle of repose for the powder blends of all batches exhibits good flow properties. Bulk Density, Tapped Density and Carr's Index were studied. From the obtained Bulk density and Tap density values Carr's index was calculated. Since the Carr's index was below 15% for all batches of powder blends, the flow property was good. The results for Angle of repose, Bulk Density, Tapped Density and Carr's Index were tabulated in Table 2.

Thickness, Diameter and Hardness

The thickness and diameter of the tablets were found in the range of 4.16 ± 0.08 to 4.33 ± 0.21 mm and 8.00 ± 0.21 to 8.10 ± 0.32 mm respectively. The hardness of the different formulations ranged from 3.66 to 4 Kg/cm^2.

Friability and Weight Variation Test

Depending upon the ingredients of different formulations, the weight of tablet was fixed. In each formulation, weight variation was within the I.P. Limit. Mostly the variation was within ± 1%. All the formulations exhibited less than 1% Friability and were within the I.P. Limit. The results are given in Table 3.

Wetting Time and Water Absorption Ratio

The results of wetting time and water absorption ratio are presented in Table 3. The wetting time was found to be least in case of Batch F2 (7sec) and maximum in case of Batch F4 (8sec) and water absorption ratio ranges from 30.18 to 35.88. Wetting time is least for CCS containing formulations and maximum for SSG containing formulations, which indicates that CCS has higher hydrophilicity compared to SSG.

Test for Uniformity of Drug Content

The content uniformity test for Pantoprazole sodium was carried out by HPLC. The results were found to be within the I.P. Limits (90-110%). It shows that the drug was distributed uniformly throughout the tablets.

***Invitro* Dispersion Time and *Invitro* Disintegration Time**

The *Invitro* dispersion time and *Invitro* disintegration time ranges from 8.75 sec (F1) to 13.50 sec (F6) and 12.50 sec (F3) to 23.50 sec (F4) respectively (Table 4). It was observed that with increase in concentration of superdisintegrant there was reduction in disintegration time. The rapid disintegration may be due to rapid uptake of water from the medium, swelling and burst effect. Also, it was observed that dispersion and disintegration time were higher for batches prepared with SSG compared to CCS. This may be due to fact that CCS is more hydrophilic than SSG, thus tablets prepared with CCS absorb water to greater extent than those prepared with SSG and disintegrate at higher rate.

***In-Vitro* Dissolution Studies**

Batches prepared with varying concentration of CCS showed release of 91.79% to 99.68% at the end of 15 minutes, whereas those prepared with SSG as superdisintegrant showed the release of 58.32% to 100.7% (Table 5). The percentage of drug release increased with increase in concentration of superdisintegrant from 5% to 15%. The higher dissolution rates observed with SSG may be due its strong swelling power which exerts sufficient hydrodynamic pressure which in turn facilitates complete and rapid disintegration. From the overall observations, formulation F_6 containing 15% w/w concentration of SSG was considered to be the optimized formulation which releases up to 100.70% of the drug in 15 minutes.

Comparative *In-vitro* Drug Release Studies

The *In-vitro* Drug release profiles for the optimized formulation F_6 (SSG-15%) was compared with Pantocid (Sun Pharmaceuticals Ltd.). At the end of 15 minutes of *invitro* dissolution study only 7.643% of the drug was released from Pantocid (Fig.1) whereas 100.70% of the drug was released from the optimized formulation F_6 (SSG-15%).

Kinetics of Drug Release

The optimized formulation F_6 upon kinetic treatment releases the drug by first order kinetics. A plot of Logarithm of percentage of drug remaining to be released versus time showed linearity. From the plot, correlation coefficient and slope value was found to be 0.998 and -0.1324. The values obtain signify that the drug release follows first order kinetics (i.e. concentration dependent release).

Table 4. *Invitro* Dispersion time and *Invitro* Disintegration time

Formulation Code	*In-Vitro* Dispersion Time (sec) ± S.D [n = 3]	*In-vitro* Disintegration Time (sec) ± S.D. [n=6]
F_1	8.75 ± 0.11	15.50 ± 0.01
F_2	9.50 ± 0.02	15.00 ± 0.13
F_3	9.50 ± 0.01	12.50 ± 0.18
F_4	14.00 ± 0.02	23.50 ± 0.14
F_5	14.00 ± 0.01	23.00 ± 0.21
F_6	13.50 ± 0.04	18.00 ± 0.12

Table 5. *Invitro* dissolution data

Time (min)	Cumulative Percentage Release					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
5	38.04	41.46	57.38	20.85	26.67	34.49
10	77.21	79.51	89.84	41.43	61.95	93.55
15	91.79	93.65	99.68	58.32	94.28	100.7

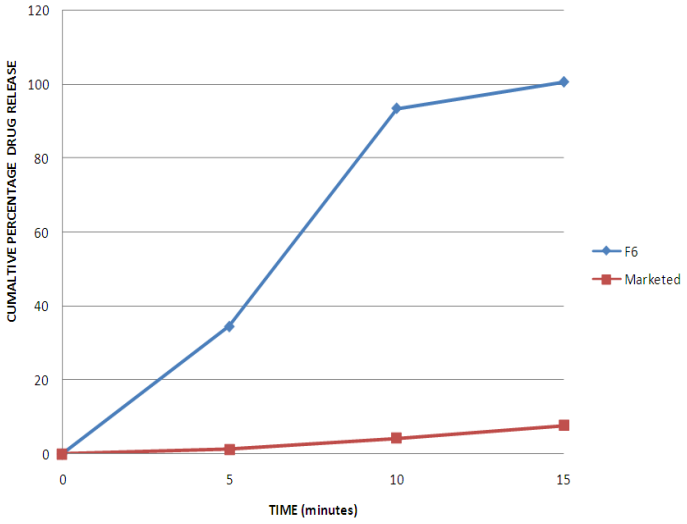

Fig.1 Comparative *Invitro* release studies of optimized formulation (F6) and marketed product

CONCLUSION

The Ora-Solv Tablets (OST's) of Pantoprazole Sodium were prepared by direct compression method using various super disintegrants such as CCS and SSG. Formulation F_6, containing 15% w/w concentration of sodium starch glycollate with appropriate amount of other excipients was considered to be the optimized formulation with the desired drug release (100.70%). Comparative drug release study revealed that the formulated Ora-Solv Tablets (OST's) release drug more rapidly than the marketed sample. They have sufficient mechanical strength, quick disintegration in mouth and good dissolution.

It was concluded that the optimized formulation F_6 followed First order kinetics, which was revealed by the linearity shown from the plot of logarithm of drug remaining to be released versus time. The Ora-Solv Tablet formulation of Pantoprazole sodium provides instant relief from Hyper-gastric disorders and helps them to resume their normal function as soon as possible. The OST's have potential advantages over conventional marketed tablets with their improved patient compliance, both in geriatrics and paediatrics, ease of administration and bio-availability.

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