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Formulation and Evaluation of Dolasetron Orally Disintegrating Tablets

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Abstract: ***The aim of present study is to formulate Dolasetron orally disintegrating tablets by using by direct compression method and evaluating its characteristics. This dosage form is more comfortable for pediatric and geriatric patients. This serves as orally dispersible system because of its convenient nature. Compared with all the excipient drugs the cross povidone shows high activity. Dolasetron along with cross povidone developed more than 95.34% drug release which show highest number of drug released compared to SSG and cross carmellose. The disintegration time is fast for cross povidone compared to others. Dolasetron might have immense effect on Anti-emetic property as per this study.***

Keywords: Dolasetron, orally disintegrating tablets, direct compression method, pediatric and geriatric patients, cross povidone

1. Introduction

Oral administration is the most mainstream study because of simplicity of ingestion, torment shirking, flexibility and in particular, quiet consistence. A few novel advances for oral conveyance have as of late become accessible to address the physiochemical and pharmacokinetic attributes of medications, while improving patient compliance.1-3 The most alluring plan for use by the older is one that is anything but difficult to swallow and simple to deal with. Mulling over these prerequisites, endeavors have been made to build up a fast dissolving tablet. Since such a tablet can break down in just a limited quantity of water in the oral dispersion.5Recently, many companies have researched and developed various types of fast-disintegrating dosage form technologies with the potential to accommodate various physiochemical, pharmacokinetic and pharmacodynamic characteristics of drugs. These tablets are also called as orodispersible tablets, quick disintegrating tablets, mouth dissolving tablets, fast disintegrating tablets, fast dissolving tablets, rapid dissolving tablets, porous tablets and rapimelts. However of all the above terms, United States of pharmacopoeia (USP) approved these dosage forms as ODTs orodispersible tablet for tablets that disperses readily within 3min in mouth before swallowing. United States of Food and Drug Administration (FDA) defined ODT as "A solid dosage form containing medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue". The disintegration time for ODTs generally ranges from several seconds to about a minute.6-9

Benefits of Rapid Dissolving Tablets

1) Convenience of administration and accurate dosing as compared to liquids.
2) No need of water to swallow the dosage form.
3) Good mouth feel property of these tablets helps to change the basic view of medication as "bitter pill", particularly for pediatric patients.
4) Rapid dissolution and absorption of drug, which may produce quick onset of action
5) Pregastric absorption can result in improved bioavailability and as a result of reduced dosage, improved clinical performance through a reduction of unwanted effects.
6) An increased bioavailability, particularly in cases of insoluble and hydrophobic drugs, dueto rapid disintegration and dissolution of tablets.

2. Materials and Methods

Sr. No.	Materials Used	Manufacturer
1	Dolasetron	Mayer healthcare pharmaceuticals, Bangalore
2	Microcrystalline cellulose	SD fine chemicals, Mumbai
3	Sodium starch glycolate	Shreeji chemicals, Mumbai
4	Cross carmellose sodium	Shreeji chemicals, Mumbai
5	Cross povidone	Shreeji chemicals, Mumbai
6	Talc	SD fine chemicals, Mumbai
7	Magnesium stearate	SD fine chemicals, Mumbai
8	Aspartame	Shreeji chemicals, Mumbai
9	Raspberry flavour	Microlabs, Bangalore
10	Potassium dihydrogen ortho phosphate	SD fine chemicals, Mumbai
11	Sodium hydroxide	SD fine chemicals, Mumbai

Preformulation studies

Preformulation testing is the first step in the rationale development of dosage forms of a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It gives extensive information to bring out good quality at high standard at which optimal dosage desired. Preformulation studies were performed on the drug (API), which included melting point determination, solubility and compatibility studies.[10] The following preformulation studies were performed for Dolasetron Hcl and polymers;

Determination of solubility

Solubility of Dolasetron was performed in solvents water and alcohol.

Determination of melting point

Melting point of pure Dolasetron was determined by open capillary method. The capillary tube was closed at one end by fusion and was filled with Dolasetron hydrochloride by repeated tapings. The capillary tube was placed in a digital melting point apparatus. The instrument was set to automatically increase the temperature of the heating bath at a rate of 100°c min rise of temperature per minute. The rise in temperature was viewed through magnifying lens. The temperature at which the drug started melting was recorded.[11-15] This was performed thrice and the average value was calculated.

Determination of λ max

A solution of Dolasetron containing conc.10µg/ml was prepared in phosphate buffer pH6.8 and UV spectrum was taken using Shimadzu (UV-1800) spectrophotometer. The solution was scanned in the range of 200-400nm[16]

Formulation development

In this work, direct compression method with the aid of super disintegrants is attempted for the formulation development of rapid dissolving tablets of Dolasetron. The Dolasetron tablets are available in 12.5mg, 25mg and 50mg doses in the market. Dose of 25mg is selected for the present study. Development of the formulation in the present study was mainly based on the type and concentration of polymers and the properties of the drug[17, 18]. Various polymers in different concentrations (3%, 5% and 7%) were used so as to get tablets with good physical properties.

Formulation of Dolasetron Orally disintegrating tablets by Direct Compressing method

S. No.	Ingredients	F1	F2	F3	F4	F5	F6
1.	SSG	3	5.25	7.5	-	-	-
2.	Cross carmellose sodium	-	-	-	-	1	3
3.	Cross povidone	-	-	-	3	5.25	7.5

Evaluation of dolasetron tablets.

1) Drug-polymer compatibility studies

In the preparation of tablets formulation, drug and polymer may interact as they are in close contact with each other, which could lead to the stability of drug. Pre-formulation studies regarding the drug-polymer interaction are therefore very critical in selecting appropriate polymers. FT-IR spectroscopy was employed to ascertain the compatibility between Dolasetron and the selected polymers. Potassium bromide, pure drug and the polymers were heated to 105◦c for 1hr to remove the moisture content if present in a hot air oven. Then in presence of IR lamp, potassium bromide was mixed with drug and / or polymer in 9: 1 ratio and the spectra were taken. FT-IR spectrum of Dolasetron was compared with FT-IR spectra of polymers.

2) Pre-compression parameters

a) Angle of Repose:

The angle of repose of the powder blend was calculated by using the following formula28 Tan θ = h / r θ = tan-1 (h / r) Where, θ = Angle of repose h = Height of the pile. r = Radius of the pile

b) Compressibility Index:

Compressibility index (%) = $TD - BDTD \times 100$ Calculated based on the following formula.

Where, TD = Tapped density, BD = Bulk density

c) Hausner's Ratio:

Calculated based on the following formula.
Hausner's ratio = $apped\ density\ /\ Bulk\ density$
The value was expressed in Kg/cm2.

d) Bulk density:

Loose bulk density (LBD) and tapped bulk density (TBD) of Dolasetron and the tablet blends were determined using bulk density apparatus. The LBD and TBD were calculated in g/ml using following formula.

LBD = weight of the powder/ volume of the packing
TBD = weight of the powder/ tapped volume of the packing

3) Post-compression parameters

a) Thickness:

The thickness of the individual tablets was measured using Vernier caliper, and the average thickness was determined. The thickness was denoted in millimeters.

b) **Weight Variation Test**:

Twenty tablets were selected at random, and their weight was noted, and from that, the mean weight of the tablets was calculated. Not more than two of the individual weights deviate from the average weight by more than the percentage deviation.

c) Friability:

Friability is the measure of tablet's ability to withstand both shock and abrasion without crumbling during manufacturing, packing, shipping and consumer use. Tablets that tend to powder, chip and fragment when handled lack elegance and consumer acceptance. The weight of 10 tablets was noted and placed in Roche friabilator. The device subjects the tablets to the combined effect of shock and abrasion by utilizing a plastic chamber that revolves at 25 rpm, rolling the tablets a distance of 6 inches with the revolution. The tablets were removed after 100 revolutions,

dedusted, and reweighed. Tablets that weigh less than 0.5 to 1 percent are generally acceptable[19]. The percentage friability of the tablets was

Percentage Friability = $InitialWeight - FinalWeight / InitialWeight$ x 100 calculated by the formula.

d) Invitro dispersion time:

Invitro dispersion time was measured by dropping a tablet into a petridish containing 10ml of phosphate buffer pH6.8 solution (simulated saliva fluid). Three tablets from each formulation were randomly selected and tested[20]. Invitro dispersion time was found and expressed in seconds.

e) Drug content determination:

Calibration of Dolasetron in phosphate buffer (pH6.8) solution at λmax249.60[21]

3. Results

Preformulation Studies

1) Determination of solubility

Dolasetron was found to be freely soluble in water and alcohol.

2) Determinationof melting point

The melting point of Dolasetron was found to be in the range of 220◦c.

3) Determination of λmax

Wavelength of maximum absorption of Dolasetron in phosphate buffer pH 6.8

Physical Parameters of Drug and Super Disintegrants

Drug/Polymer	Bulk density (g/cc)	Tapped Density (g/cc)	Angle of Repose (Θ)	Carr's Index	Hausner ratio
SSG	0.54	0.46	25°22'	19.45	1.36
Crosscarmellose	0.49	0.48	23°65'	17.66	1.21
Cross povidone	0.58	0.41	20°65'	19.38	1.26

Evaluation of Dolasetron Tablets

Precompression Parameters of Dolasetron Tablets:

Formulation Code	Bulk density (g/cc)	Tapped density (g/cc)	Angle of Repose (Θ)	Carr's Index	Hausner ratio
PF1	21.02±1.64	0.58±0.001	0.66±0.015	16.85±1.50	1.18±0.01
PF2	23.08±2.73	0.56±0.002	0.62±0.008	17.36±1.71	1.16±0.04
PF3	25.77±1.04	0.55±0.004	0.68±0.022	13.46±1.43	1.15±0.04
PF4	26.03±0.35	0.54±0.004	0.64±0.010	21.71±0.63	1.21±0.04
PF5	24.88±0.76	0.58±0.004	0.65±0.008	21.85±1.11	1.22±0.03
PF6	24.54±0.70	0.56±0.002	0.63±0.007	22.92±1.05	1.23±0.03

Value expressed as mean ±*SD*, *n*=3

Post-Parameter Evaluation:

Results of thickness, hardness, friability and weight variation of Dolasetrontablets

Formulation code	Thickness (mm)	Hardness (kg/cm ²)	Friability (%)	Weight variation
PF1	2.32±0.01	3.4±0.38	0.52	148.10±0.20
PF2	2.56±0.07	3.5±0.33	0.45	155.09±0.33
PF3	2.88±0.02	3.5±0.65	0.49	151.19±0.21
PF4	2.53±0.05	4.3±0.25	0.77	149.33±1.76
PF5	2.43±0.01	3.9±0.31	0.79	148.80±1.03
PF6	2.46±0.05	3.9±0.72	0.66	156.33±2.12

Value expressed as mean ±*SD*, *n*=3

Results of in vitro dispersion time, wetting time and water absorption ratio of Dolasetron tablets

Formulation code	In vitro dispersion time (sec)	Wetting time (sec)	Water absorption ratio
PF1	58.40±4.13	69.33±3.51	79.38±1.91
PF2	56.33±4.16	65.13±3.81	81.65±1.10
PF3	41.33±3.18	44.12±3.21	88.54±1.52
PF4	55.21±3.10	61.65±3.00	79.72±1.98
PF5	49.11±4.10	56.00±4.00	85.41±1.23
PF6	44.33±3.11	49.33±3.11	94.72±2.00

Value expressed as mean ±*SD*, n=3

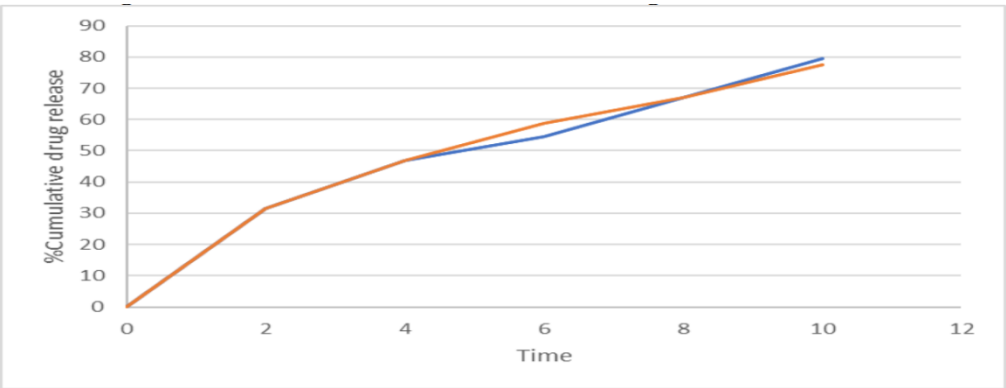
Determination of drug content of Dolasetron tablets

SR. No.	Concentration (µg/ml)	Absorbance at 249.60nm
1	2	0.286
2	4	0.456
3	6	0.665
4	8	0.715
5	10	0.898

In vitro drug release profile of Dolasetron tablets containing SSG

SR. NO.	Time (min)	% Cumulative drug release	
		PF1	PF2
1	0	0	0
2	2	30.13 ±0.65	36.87 ±0.21
3	4	34.88 ±1.12	43.97 ±1.12
4	6	45.70 ±1.23	49.60 ±0.76
5	8	53.64 ±0.76	54.85 ±0.76
6	10	59.75 ±0.98	64.77 ±0.75

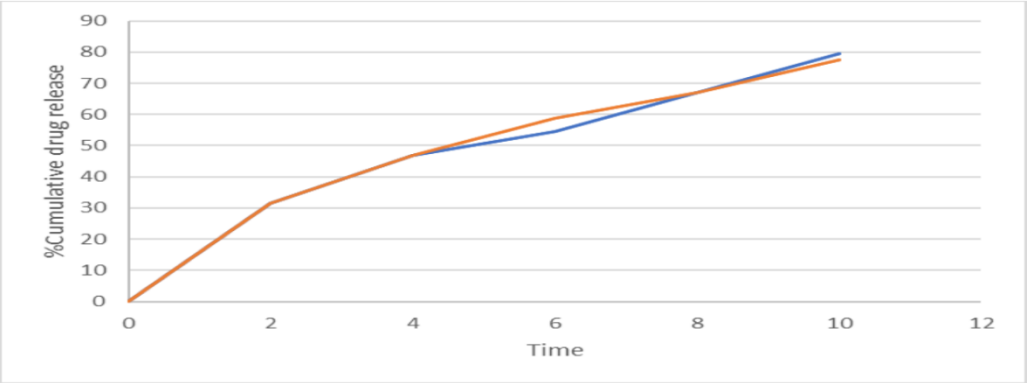
In vitro drug release date of Dolasetron tablets containing SSG



In vitro drug release date of Dolasetron tablets containing Cross carmellose sodium

Sr. No.	Time (min)	% Cumulative drug release	
		PF3	**PF4**
1	0	0	0
2	2	31.67±0.23	36.89±0.34
3	4	46.92±0.67	45.88±1.45
4	6	58.64±0.65	58.83±1.00
5	8	66.88±0.78	66.10±1.32
6	10	75.58±1.15	79.87±0.78

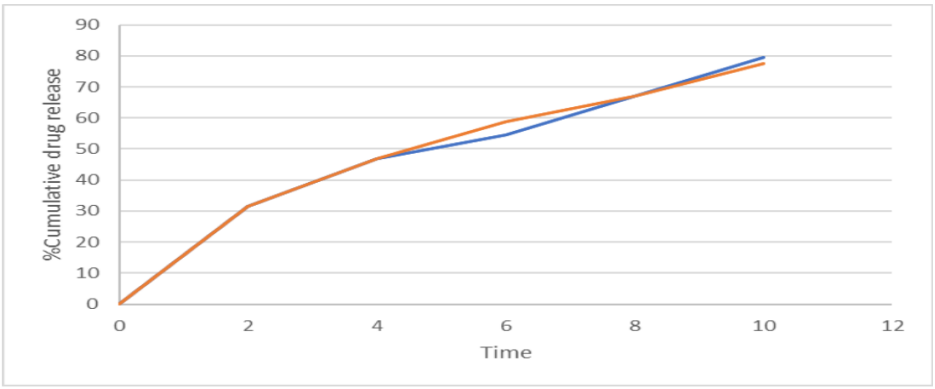
Invitro drug release data of Dolasetron tablets containing Cross carmellose sodium



Invitro drug release data of Dolasetron tablets containing Cross povidone

Sr. No.	Time (min)	% Cumulative drug release	
		PF5	PF6
1	0	0	0
2	2	41.76±0.76	42.72±0.73
3	4	56.87±0.43	56.98±0.54
4	6	78.50±1.32	73.65±0.32
5	8	85.92±1.12	88.64±0.65
6	10	93.43±0.63	95.34±1.34

Invitro drug release data of Dolasetron tablets containing Cross povidone



4. Discussion

- Six formulations were designed, using super disintegrants. SSG Crosspovidone and cross carmellose were used as the super disintegrants. For each designed formulation, blend of drug and excipients were prepared and evaluated for precompression parameters. The results indicate the good flow properties of the blend.
- Tablets were prepared by direct compression technique. As the material was free flowing, tablets of all formulations were obtained of uniform weight due to uniform die fill, compiled with pharmacopeia limits. Hardness of the tablet is kept within 35kg/cm². Friability of the formulations were below 1.0% was an indication of good resistance of tablets.
- Water absorption ratio which is an important criterion for understanding the capacity of disintegrants to swell in presence of little amount of water, was calculated and was in the range of 65-95%. The time required for the drug to be released is 30minutes. Invitro dispersion time was 7-25seconds for formulations containing SSG, Cross carmellose sodium and Cross povidone. Amount of drug dispersed was determined.
- The wetting time of all the formulations (PF1-PF6) were found to be within 44.3470.22 seconds, which complies with the official specifications. The results were showed the water absorption ratio of all the formulated batches was found to be 7995% which was satisfactory in giving effective and better formulations of rapid dissolving tablets.

Invitro drug release study

Total six formulations were formulated PF1-PF6 by using three different super disintegrants in varying concentrations. The formulations PF1-PF2 were formulated with the help of sodium starch glycolate in concentration 3%, 5%, 7% respectively. The formulations PF3-PF4 were formulated with the help of cross carmellose in concentration 3%, 5%, 7% respectively and the formulations PF5-PF6 were formulated with the help of cross povidone in concentrations 3%, 5%, 7% respectively. The formulations PF5-PF6 containing crosspovidone showed more than 90% drug release. Among those three the formulation PF6

showed highest drug release of 95.34%. The data for invitro drug release of formulations were determined.

5. Conclusion

From the study carried out on Dolasetron oral dispersible tablet using by direct compression method, the following conclusion can be drawn. The Pre formulation study gives the following information of optimize batch Angle of Repose-25.65" Bulk density-0.58, Tapped density-0.41, Compressibility Index-19.38 good to flow, Hausner ratio-1.26. Post parameter evaluation of tablets Hardness-3.9, Friability-0.66, Thickness-2.460, Weight variation-156.33 ±, Dispersion time-44sec, Water absorption ratio-94.72, In-vitro drug release studies-in 2min. Compared with all the excipient drugs the cross povidone shows high activity. Dolasetron along with cross povidone developed more than 95.34% drug release which shows highest number of drug released compared to SSG and cross carmellose. The disintegration time is fast for cross povidone compared to other. In future study it is evident that it can be forecasted for advance reaction and clinical trails. Dolasetron might have immense effect on Anti-emetic property as per this study.

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