Asian Journal of Pharmaceutical Education and Research
Vol -8, Issue-4, October-December 2019
ISSN:2278 7496

RESEARCH ARTICLE Impact Factor: 7.014

FORMULATION DEVELOPMENT AND EVALUATION OF FAST DISSOLVING ORAL FILM OF DOLASETRON MESYLATE

Abhishek Kumar*, Richa Verma, Vivek Jain

NRI Institute of Pharmaceutical Sciences, Bhopal (M.P.)

*Corresponding Author's E mail: abhishekkumarssm67@gmail.com

Received 23 Aug 2019; Revised 25 Aug 2019; Accepted 06 Sept 2019, Available online 15 Oct. 2019

ABSTRACT

The aim of present work is to formulate and evaluate fast dissolving oral films of dolasetron mesylate to improve water solubility, dissolution rate, oral bioavailability and reduction of first pass metabolism and increase patient's compliance. Oral fast dissolving films prepared by solvent casting method using water and 95% ethanol as solvents and HPMC as film forming polymer. PEG 400 was the selected plasticizers, Superdisintegrants such as croscarmellose sodium (CCS) and sodium starch glycolate (SSG) alone and also in combinations was incorporated to achieve the aim. The prepared films were evaluated for the drug content, weight variation, film thickness, disintegration time, folding endurance, percentage of moisture content and *in vitro* dissolution studies and taste mask studies on healthy human volunteers. Among all, the formulation F3 was found to be best formulation which releases 99.12% of the drug within 15 min and disintegration time is 47±7 sec. which was significantly high when compared to other formulation. The data obtained from In-vitro release were fitted into the various kinetic models such as Zero Order, Higuchi, First Order and Korsmeyer–Peppas model in order to determine the mechanism of drug release. When the regression coefficient values compared, it was observed that 'r' values of formulation F3 was maximum i.e 0.951hence indicating drug release from formulations was found to follow first order drug release kinetics.

K**eywords:** Dolasetron Mesylate, Antiemetic activity, Fast dissolving films, Solvent casting method.

INTRODUCTION:

Rapidly dissolving or quick dissolving dosage forms have acquired great importance in the pharmaceutical industry due to their unique properties and advantages [1,2]. They undergo disintegration in the salivary fluids of the oral cavity within a minute, where they release the active pharmaceutical ingredient. The major amount of the active pharmaceutical ingredient is swallowed orally with the saliva where subsequent absorption takes place in the gastrointestinal tract [3,4]. The rapidly dissolving dosage forms are referred by various names by researchers like quick disintegrating, orally disintegrating, mouth dissolve or melt in mouth dosage forms [1,3,4]. These dosage forms possess certain specific advantages like no need of water for disintegration, accurate dosing, rapid onset of action, ease of transportability, ease of handling, pleasant taste and improved patient compliance. United States Food and Drug Administration (USFDA) defined the fast dissolving oral thin films as a thin, flexible, non-friable

polymeric film strip containing one or more dispersed/dissolved active pharmaceutical ingredients, which is intended to be placed on the tongue for rapid *in vitro* disintegration or dissolution in the saliva prior to swallowing for delivery into the gastrointestinal tract [5]. Dolasetron is a 5-HT3 antagonist used in the prophylaxis treatment for women with predominant irritable bowel syndrome (IBS) [6,7]. IBS is a gastrointestinal disorder characterized by abdominal pain, distressed bowel function and abdominal distension dolasetron was included in the United States Pharmacopeia (USP) prioritized list of chemical medicine monographs in 2013 [8]. Dolasetron is chemically (1s,3R,5r,7S)-10-oxo-8-azatricyclo [5.3.1.0] undecan-5-yl 1H-indole-3-carboxylate. The molecular formula is $C_{19}H_{20}N_2O_3$ and molecular weight 324.38 g/mol. The objective of the present research work was to develop fast dissolving oral films of dolasetron disintegrating within 47s to enhance the convenience of administration to the patients to improve compliance. The formulation developed was simple, easy to prepare and economical with great applicability and also giving faster *in vitro* drug dissolution rate as compared to the commercially available immediate release tablets.

MATERIALS AND METHODS

Materials

Dolasetron was obtained as a gift sample from Hetero Drugs Ltd Hyderabad. HPMC was procured from Qualikems fine chem. Pvt Ltd Vadodhara. PEG400, sodium starch glycolate, croscarmellose sodium was obtained from S.D fine chemicals limited, Mumbai. Citric acid, ethanol was obtained from Loba Chemical Pvt Ltd (Mumbai, India). Hydrochloric acid, KH_2 PO_4, NaoH was obtained from S. D. Fine Chem. Ltd., Mumbai. All other chemical were purchased from Hi Media, Mumbai. Double distilled water was prepared freshly and used whenever required. All the chemicals used in this work were of analytical grade.

Standardization of Dolasetron by UV-Visible spectrophotometry

Preparation of stock solution: Stock solution 1000µg/ml dolasetron was prepared in 0.1 N Hcl solutions. This solution was suitably diluted with 0.1 N Hcl solutions to obtain a concentration of 15µg/ml. The resultant solution was scanned in the range of 200-400 nm using UV double beam spectrophotometer (Labindia 3000+, Mumbai).

Standard calibration of dolasetron: From stock solutions of dolasetron 1 ml was taken and diluted up to 10 ml. from this solution 0.5, 1.0, 1.5, 2.0 and 2.5 ml solutions were transferred to 10ml volumetric flasks and make up the volume up to 10 ml with 0.1 N Hcl, gives standard drug solution of 5, 10, 15, 20, 25µg/ ml concentration, absorbance was measured at 281nm.

Formulation development of oral film of dolasetron

Solvent casting technique

Drug (Dolasetron mesylate) containing fast dissolving films were fabricated by the solvent casting method [9]. The optimized amount of HPMC was dissolved in 5ml of water and stirrer continuously for 1 hour, optimized amount of Plasticizer and drug were dissolved in 95% ethanol and then added to the polymeric solution, the optimized amount of drug was dissolved in 2ml of water and kept on sonication for proper dispersion. Polymeric solution was stirred for 30 min using magnetic stirrer and was kept in undisturbed condition till the entrapped air bubbles were removed. The aqueous solution was casted in a glass moulds having 2.5 x 2.5 cm * 10 films area and was dried at controlled room temperature (25°-30°C, 45 %RH) as well as at increased temperature (microwave oven). The film took approximately 48 hr to dry at controlled room temperature. The dried film was carefully removed from the glass plates and was cut into size required for testing. The films were stored in air tight plastic bags till further use. The compositions of the formulations were shown in table 1 and 2.

Table 1 Selection and Optimization of Film Forming Agents

Name of ingredients	F1	F2	F3	F4	F5	F6
API	50	50	50	50	50	50
HPMC	50	100	150	50	100	150
Glycerin	-	-	-	-	-	-
PEG-400	10	10	10	10	10	10
SSG	20	20	20			
CS	-	-	-	20	20	20
Aspartame	5	5	5	5	5	5
Citric acid	10	10	10	10	10	10
DM water qs to	-	-	-	-	-	-

Table 2 Optimization of Concentration of super disintegrant

Name of ingredients	F1	F2	F3	F4	F5	F6
API	50	50	50	50	50	50
HPMC	150	150	150	150	150	150
Glycerin	-	-	-	-	-	-
PEG-400	10	10	10	10	10	10
SSG	20	30	40			
CS	-	-	-	20	30	40
Aspartame	5	5	5	5	5	5
Citric acid	10	10	10	10	10	10
DM water qs to	-	-	-	-	-	-

Evaluation

The formulations were evaluated by the following tests [10-13].

Thickness

Randomly 10 films were selected and thickness was measured using vernier calliper at three different places.

Weight variation

For each formulation, three randomly selected patches were used. For weight variation test, 10 films from each batch were weighed individually by digital electronic balance and the average weight was calculated.

Folding endurance

This was determined by repeatedly folding one film at the same place until it broke. The number of times the film could be folded at the same place without breaking cracking gave the value of folding endurance.

Percentage of moisture content

The films were weighed individually and kept in desiccators containing activated silica at room temperature for 24 hrs. Individual films were weighed repeatedly until they showed a constant weight. The percentage of moisture content was calculated as the difference between initial and final weight with respect to final weight.

Drug content analysis

The patches (n = 3) of specified area were taken into a 10 ml volumetric flask and dissolved in methanol and volume was made up with 10 ml methanol. Subsequent dilutions were made and analyzed by UV spectrophotometer at 281nm.

Disintegrating time

The most important criteria of present work are to that dosage form should be dissolved within few seconds. The incorporation of super disintegrating agent to minimizes the disintegrating time. Three super disintegrating agent were selected for this work. The film of (4.15cm2) size (unit dose) was placed on a petridish containing 10 ml of distilled water. The time required for the film to break was noted as cursive *in vitro* disintegration time.

In vitro dissolution study

The *in vitro* dissolution test was performed using the USPXXX dissolution apparatus II (Paddle with sinker). The dissolution studies were carried out at 37±0.5° C; with stirring speed of 50 rpm in 900 ml 0.1 N Hydrochloric acid. Film size required for dose delivery (2.5×2.5 cm^2) was used. Five ml aliquot of dissolution media was collected at time intervals of 1, 2, 5, 10 and 15 minutes and replaced with equal volumes of 0.1 N HCl. The collected samples were filtered through 0.45 μm membrane filter and the

concentration of the dissolved Dolasetron mesylate was determined using UV-Visible spectrophotometer at 281 nm. The results were presented as an average of three such concentrations.

Stability studies

Stability studies were carried out with optimized formulation which was stored for a period of one, two and three months at 40±2^{o}C temperature and 75±5% relative humidity for a period 3 months. The % Assay of formulation was determined by U.V. spectrophotometer using calibration curve method. The % assay of film was found to slightly decrease at higher temperature.

Results and Discussion

λ_{max} of dolasetron was found to be 281 nm in 0.1 N Hcl solution by using U.V. spectrophotometer (Labindia-3000+) Fig. 1. The calibration curve of dolasetron was found to be linear in the concentration range of 5-25µg/ml at 281nm. The general appearance, assay, weight variation and thickness of all the films were within acceptable limits table 3. The results for tensile strength, folding endurance, disintegrating time and % of moisture were shown in table 4. Tensile strength value of optimized formulation (F3) was 1.245±0.145kg/cm^2 and folding endurance was more than 150. The assay values of all the formulations were ranging from 97.98±0.25 to 99.89±0.36 %. The disintegration time was ranging between 45±4 to 50±5 sec. The final formulation shows better drug release (99.12%) compared to other formulation within 15 min (table 5). The cumulative percentage (%) drug release profile and the assay of the F3 formulation films indicates that the drug remain stable under the ASC without any significant change in its release profile and the drug content. From the stability studies it was clearly observed that the drug showed good stability after subjecting to accelerated stress conditions and the polymers shown significantly compatibility with the drug. The kinetic data of optimized formulation F3 was given in table 6and Fig 2, 3. It was fallow first order drug release kinetics.

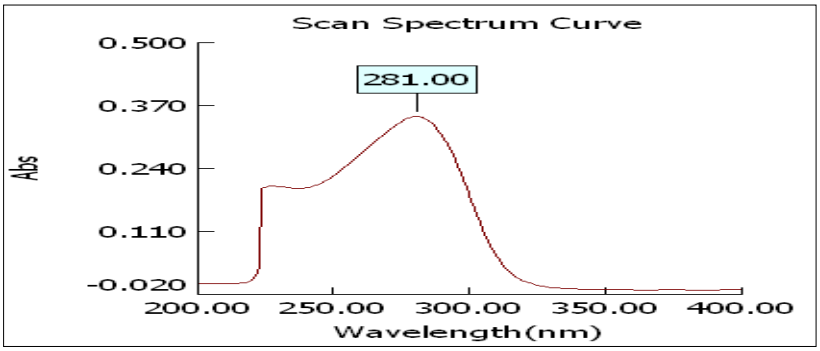

Figure 1 Determination of λ_{max} of Dolasetron mesylate

Table 3 Result of general appearance, thickness, weight variation and % assay

Formulation code	General Appearance	Thickness in µm	Weight mg	% Assay
F1	Translucent	50±4	230±4	98.89±0.15
F2	Translucent	52±3	235±6	97.98±0.25
F3	Translucent	53±5	240±8	99.89±0.36
F4	Translucent	54±6	230±9	98.12±0.25
F5	Translucent	52±4	235±8	98.98±0.14
F6	Translucent	51±2	236±4	98.45±0.15

Table 4 Result of folding endurance, disintegrating time, tensile strength &% of moisture content

Formulation code	Folding endurance (Times)	Disintegrating time (Sec.)	Tensile strength in kg/cm^2	Percentage of Moisture Content
F1	More than 150	45±4	1.125±0.250	0.698±0.125
F2	More than 150	48±6	1.210±0.351	0.647±0.145
F3	More than 150	47±7	1.245±0.145	0.897±0.415
F4	More than 150	46±6	1.289±0.365	0.998±0.147
F5	More than 150	49±4	1.312±0.458	0.154±0.178
F6	More than 150	50±5	1.315±0.178	0.780±0.325

Table 5 Results of *In-Vitro* release study of optimized formulation F3

S. No.	Time (Min.)	% CDR
1.	1	48.98
2.	2	65.56
3.	5	75.58
4.	10	98.25
5.	15	99.12

Table 6 Kinetics data of optimized formulation F3

Formulation	Regration Coefficient	Zero order	First order
F3	r^2	0.866	0.951

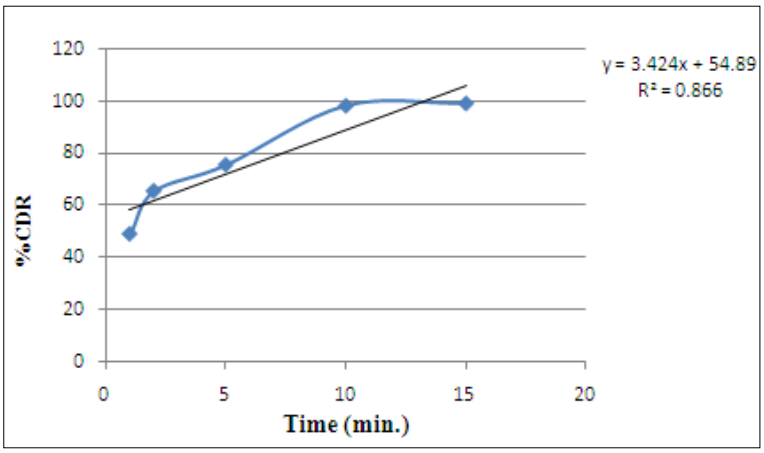

Figure 2 Zero order release kinetics of optimized formulation F3

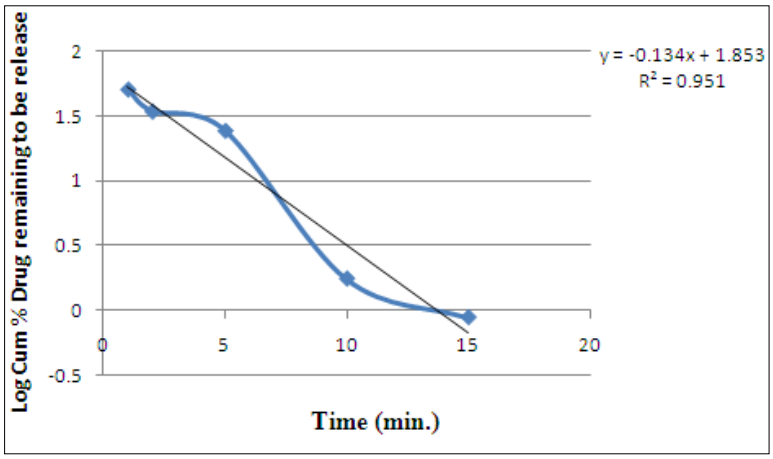

Figure 3 First order release kinetics of optimized formulation F3

CONCLUSION

The present study indicates a good orally fast dissolving films containing Dolasetron mesylate for systemic delivery with an added advantage of faster drug action for prevention of nausea and vomiting associated with moderately-emetogenic cancer chemotherapy and for the prevention of postoperative nausea and vomiting. Finally, it is concluded that the drug release from the fast dissolving film was increased by using the increased concentration of Superdisintegrant, thus assisting in faster disintegration in the buccal cavity. As the drug having low solubility, fast disintegration may leads to more drug availability for dissolution, resulting in faster absorption in systemic circulation increased systemic availability of drug may leads to quick onset of action which is prerequisite for nausea and vomiting.

References

1. Liang AC, Chen LH. Fast-dissolving intraoral drug delivery systems. ExpOpinTher Patents. 2001; 11:981–6.

2. Borsadia S, O'Halloran D, Osborne JL. Quick dissolving films-A novel approach to drug delivery. Drug DelivTechnol. 2003; 3:63-6.
3. Klancke J. Dissolution testing of orally disintegrating tablets. Dissolut Technol. 2003; 10:6–8.
4. Parakh SR, Gothoskar AV. Review of mouth dissolving tablet technologies. Pharm Tech. 2003; 27:92–100.
5. http:// www.access data. fda. gov/drugsatfda_docs/ nda/2015/022524orig1s000chemr.pdf.
6. Diemunsch P, Leeser J, Feiss P, D'Hollander A, Bradburn BG, Paxton D, et al. Intravenous dolasetron mesilate ameliorates postoperative nausea and vomiting. Can J Anesth. 1997; 44:173-81. 2.
7. Philip BK, Pearman MH, Kovac AL, Chelly JE, Wetchler BV, McKenzie R, et al. Dolasetron for the prevention of postoperative nausea and vomiting following outpatient surgery with general anaesthesia: a randomized, placebo-controlled study. The Dolasetron PONV Prevention Study Group. Eur J Anaesthesiol. 2000; 17:23-32. 3.
8. Graczyk SG, McKenzie R, Kallar S, Hickok CB, Melson T, Morrill B, et al. Intravenous dolasetron for the prevention of postoperative nausea and vomiting after outpatient laparoscopic gynecologic surgery. Anesth Analg. 1997; 84:325-30
9. K. Senthilkumar and C. Vijaya. Formulation development of mouth dissolving film of etoricoxib for pain management. Advances in Pharmaceutics. 2015, Article ID 702963,.
10. Kumar GV, Krishna RV, William GJ, Konde A. Formulation and evaluation of buccal films of Salbutamol sulphate. Ind J Pharm Sci. 2005; 67: 160–164.
11. Mona Nagar, Mayank Nagar and Vikram Chopra, Formulation and evaluation of mouth dissolving film of antipsychotic drug aripiprazole, Der Pharm Lett. 2012; 4 (4): 1221- 1227.
12. Prabhu P, Malli R, Koland M, Vijaynarayana K, D'Souza U, Harish NM, Shastry CS. Formulation and evaluation of fast dissolving films of levocetrizine dihydrochloride, Int J Pharm Inves. 2011;1(2): 99–104. 17.
13. Nafee NA, Boraie MA, Ismail FA, Mortada LM. Design and characterization of mucoadhesive buccal patches containing cetylpyridinium chloride. ACTA Pharm. 2003; 53: 199–212.