ISSN: 2349-5448

Intercontinental Journal of Pharmaceutical Investigations and Research (ICJPIR)

ICJPIR |Vol.11 | Issue 1 | Jan - Mar -2024

www.icjpir.com

DOI : https://doi.org/10.61096/icjpir.v11.iss1.2024.13-19

Research

Development and evaluation of everolimus fast dissolving tablets

Adulapuram Tejaswini[1], Nallabelly Laxmi[2], Dr. Pancheddula Munija[*]

**Vice Principal, Vision college of Pharmaceutical Sciences & Research, Boduppal, Hyderabad-500092*
1,2 Asisstant professor , Vision college of Pharmaceutical Sciences & Research, Boduppal, Hyderabad-500092, India.

*Author for Correspondence: P. Munija
Email: munijapharma@gmail.com

Published on: 07 Mar 2024

Published by:
DrSriram Publications

Abstract

Recent developments in Fast Dissolving tablets have brought convenience in dosing to pediatric and elderly patients who have trouble in swallowing tablets. The objective of the present study was to prepare the Fast Dissolving tablets of Everolimus, It is currently used as an immunosuppressant to prevent rejection of organ transplants and in the treatment of renal cell cancer and other tumours. Hence, the present investigation was undertaken with a view to develop a Fast Dissolving tablet of Everolimus which offers a new range of products having desired characteristics and intended benefits. Super disintegrants such as Ac-Di-Sol was used. Drug-excipient compatibility studies were carried. The tablets were prepared by direct compression technique. The tablets were evaluated for hardness, friability, weight variation, disintegration time, and uniformity of content and *in vitro* dissolution. It was concluded that Fast Dissolving tablets of Everolimuswere formulated successfully with desired characteristics which disintegrated rapidly and enhanced the patient convenience and compliance.

Keywords: Everolimus, Fast Dissolving Tablets, Polyplasdone XL, Ac-Di-Sol, PEG-4000.

INTRODUCTION

Drug delivery systems are a magic tool for expanding markets. DDS make a significant contribution to global pharmaceutical sales through market segmentation, and are moving rapidly. Fast disintegrating drug delivery (FDDTs,) can be achieved by various conventional methods like direct compression, wet granulation, moulding, spray drying, freeze drying, sublimation. In order to allow fast disintegration of tablets , they are made of either very porous and soft molded matrices or compressed into tablets with very low compression force. The oral fast-disintegrating tablets is also known as fast dissolve, rapid dissolve, rapid melt and quick disintegrating tablets. However, the function and concept of all these dosage forms are similar. By definition, a solid dosage form that dissolves or disintegrates quickly in the oral cavity, resulting in solution or suspension without the need for the ministration of water, is known as an oral fast- dispersing dosage form. According to European Pharmacopoeia, the ODT should disperse/disintegrate in less than three minutes. Difficulty in

swallowing (dysphagia) is common among all age groups, especially in elderly, and is also seen in swallowing conventional tablets and capsules.

Need to formulate mouth dissolving tablets

The need for non-invasive drug delivery systems continues due to patient's poor acceptance and compliance with existing deliveryregimens, limited market size for drug companies and drug uses coupled with high cost of disease management. MDT is one such dosage form which is useful for

- Geriatric patients mainly suffering from conditions like hand tremors and dysphasia.
- Pediatric patients who are unable to swallow easily because their central nervous system and internal muscles are not developed completely.
- Traveling patients suffering from motion sickness and diarrhoea that do not have easy access to water.
- Patients with persistent nausea for a long period of time are unable to swallow. Especially cancer patients after taking their chemotherapy are too nauseous to swallow the H_2 blockers, which are prescribed in order to avoid gastric ulceration.
- Mentally challenged patients, bed ridden patients and psychiatric patients.

METHODOLOGY

Drug-Excipients compatibility studies

Drug excipients compatibility studies were carried out by mixing the drug with various excipients in different proportions in 1:1 ratio were to have maximum likelihood interaction between them was placed in a vial and closed with rubber stopper and sealed properly. Fourier Transform Infrared Spectroscopy (FTIR) studies were performed on drug, optimized formulation using Bruker FTIR. The samples were analyzed between wave numbers 4000 cm^{-1} and 550 cm^{-1}.

Formulation development

- Drug and different concentrations of super disintegrants (Polyplasdone XL, Ac-Di-Sol and PEG-4000) and required ingredients were accurately weighed and passed through a 40-mesh screen to get uniform size particles and mixed in a glass motor for 15 min.
- The obtained blend was lubricated with magnesium stearate and glidant (Aerosil) was added and mixing was continued for further 5 min.
- The resultant mixture was directly compressed into tablets by using punch of rotary tablet compression machine. Compression force was kept constant for all formulation.

Table 1: Formulation table showing various compositions

INGREDIENTS	FORMULATION CHART								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Everolimus	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Polyplasdone XL	3	6	9	-	-	-	-	-	-
Ac-Di-Sol	-	-	-	3	6	9	-	-	-
PEG-4000	-	-	-	-	-	-	3	6	9
Lactose	77.5	74.5	71.5	77.5	74.5	71.5	77.5	74.5	71.5
Aspartame	10	10	10	10	10	10	10	10	10
Magnesium stearate	5	5	5	5	5	5	5	5	5
Aerosil	4	4	4	4	4	4	4	4	4
Total Weight	100	100	100	100	100	100	100	100	100

The tablets were prepared by using tablet compression machine.

Evaluation of tablets

Pre compression parameters

Measurement of Micromeritic properties of powders.

Angle of repose

The angle of repose of API powder is determined by the funnel method. The accurately weighed powder blend is taken in the funnel. The height of the funnel is adjusted in a way that the tip of the funnel just touched the apex of the powder blend. The powder blend is allowed to flow through the funnel freely on to the surface. The diameter of the powder cone is measured and angle of repose is calculated using the following equation.

tan Θ= h/r ……(1)
Where, h and r are the height and radius of the powder cone.

Table 2: Flow Properties and Corresponding Angle Of Repose

Flow Property	Angle of Repose (^{0})
Excellent	25-30
Good	31-35
Fair- aid not needed	36-40
Passable-may hang up	41-45
Poor-must agitate, Vibrate	46-55
Very Poor	56-65
Very, very Poor	>66

Bulk density
The powder sample under test is screened through sieve No.18 and the sample equivalent to 25 gm is weighed and filled in 100 ml graduated cylinder and the powder is levelled and the unsettled volume , V_0 is noted . The bulk density is calculated in g/cm^3 by the formula.
Bulk density = M/V_0 ……. (2)
V_0 = apparent unstirred volume
M= Powder mass

Tapped density
The powder sample under test is screened through sieve No. 18 and the weight of the sample equivalent to 25 gm filled in 100ml graduated cylinder . The mechanical tapping of cylinder is carried out using tapped density tester at a nominal rate for 500 times initially and the tapped volume V_0 is noted . Tappings are proceeded further for an additional tapping 750 times and tapped volume , V_b is noted. The difference between two tapping volume is < 2%, V_b is considered as a tapped volume V_f .The tapped density is calculated in g/cm^3 by the formula.
Tapped density = M/V_f …… (3)
M = weight of sample powder taken
V_f = Tapped volume

Compressibility index
The compressibility index of the powder blend is determined by Carr's index to know the flow character of a powder . This formula for Carr's index is as below :
Carr's Index (%) = [(TD-BD)/TD] x100 …… (4)

Hausner's ratio
The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material. The ratio of tapped density to bulk density of the powders is called the Hausner's ratio. It is calculated by the following equation.
H = Pt / ρB ……(5)
where ρT= tapped density, ρB = bulk density

Table 3: Scale of Flow ability

Compressibility index (%)	Flow character	Hausner Ratio
≤ 10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very Poor	1.46-1.59
> 38	Very, very Poor	> 1.60

Post compression parameters
Thickness
The thickness of the tablets was determined by using Digital micrometer. 10 individual tablets from each batch were used and the results averaged.

Weight variation
Twenty tablets were randomly selected from each batch and individually weighed . The average weight and standard deviation 3 batches were calculated. It passes the test for weight variation test if not more than 2 of the individual tablet weights deviate from the average weight by more than the allowed percentage deviation and none deviate by more than twice the % shown. It was calculated on an electronic weighing balance.

Friability
The friability values of the tablets were determined using a Roche-friabilator .Accurately weighed six tablets were placed in the Roche friabilator and rotated at 25 RPM for 4 min. Percentage friability was calculated using the following equation.
Friability = ([w_0-w]/w_0) x 100
Where w_0 = weight of tablet at time zero before revolution.
w = weight of the tablet after 100 revolutions

Drug content
The content of drug carried out by 5 randomly selected tablets of each formulation . The 5 tablets were grinded to get powder , this powder was dissolved in pH 6.8 phosphate buffer by sonication for 30 min and filtered through filter paper . The drug content was analysed spectrophotometrically at 278nm using UV spectrophotometer . Each measurement was carried out in triplicate and the average drug content was calculated.

Disintegration test
Six tablets were taken randomly from each batch and placed in USP disintegration apparatus baskets . Apparatus was run for 10 min. and the basket was lift from the fluid, observe whether all of the tablets have disintegrated.

Dissolution test of Everolimus
Drug release from Everolimus tablets was determined by using dissolution test USP 24 type II (paddle). The parameters used for performing the dissolution were pH 6.8 medium as the dissolution medium of quantity 900 ml. The whole study is being carried out at room temperature of 37˚ C and at a speed of 75 RPM. 5 ml aliquots of dissolution media were withdrawn each time intervals (5, 10,15 , 20 , 30 , min) and appropriate dilution by UV spectrophotometer . The concentration was calculated using standard calibration curve.

RESULTS AND DISCUSSION

Pre-Compresion Parameters Of Powder Blend

Table 4: Evaluation of pre-compression parameters of powder blend

Formulation code	Angle of repose	Bulk density(gm/mL)	Tapped density (gm/mL)	Carr's index(%)	Hausner's ratio
F1	28.19± 1.20	0.53±0.03	0.63±0.0	15.46 ±0.25	1.22±0.08
F2	16.13±0.19	0.55±0.17	0.49±0.35	14.28±0.28	1.16±0.01
F3	18.04±0.12	0.52±0.15	0.59±0.52	11.86±0.16	1.13±0.02
F4	14.31±0.17	0.47±0.18	0.53±0.42	11.32±0.12	1.12±0.03
F5	15.08±0.23	0.44±0.15	0.51±0.63	13.72±0.18	1.15±0.01
F6	23.12±0.15	0.54±0.12	0.63±0.42	14.28± 0.11	1.16±0.03
F7	15.93±0.15	0.47±0.13	0.55±0.36	14.54± 0.13	1.17±0.01
F8	19.43±0.17	0.41±0.11	0.47±0.33	12.76± 0.25	1.14±0.03
F9	13.64±0.15	0.53±0.12	0.59±0.43	10.16± 0.31	1.11±0.02

- For each formulation blend of drug and excipients were prepared and evaluated for various pre compression parameters.
- The bulk density of all formulations was found in the range of 0.41±0.11 - 0.55±0.17 and tapped densiy was in the range of 0.47±0.33- 0.63±0.42.
- The Carr's index and Hausner's ratio was calculated from tapped density and bulk density.

Post Compression Parameters Of Everolimus ODTs

Table 5: Evaluation of post compression parameters of Everolimus Fast disintegrating tablets

Formulation codes	Average weight(mg)	Hardness (kg/cm^2	Friability (%loss)	Thickness (mm)	Drug content (%)	*In vitro* disintegration Time(min)
F1	98.36	3.9	0.35	2.69	97.12	2
F2	97.32	3.1	0.48	2.90	99.59	1
F3	99.25	3.6	0.19	2.73	95.32	3
F4	97.89	3.5	0.25	2.64	98.26	1
F5	99.48	3.8	0.45	2.95	97.39	3
F6	96.52	3.2	0.53	2.86	99.76	4
F7	99.73	3.7	0.17	2.74	98.62	2
F8	98.47	3.2	0.29	2.69	97.31	1
F9	97.85	3.4	0.62	2.78	98.43	3

Weight variation and Thickness: All the formulations were evaluated for uniformity of weight using electronic weighing balance and the results are shown above.

Hardness and friability: All the FDT formulations were evaluated for their hardness using Monsanto hardness tester and the results are shown above. The average hardness for all formulations was found to be between (3.1 - 3.9) kg/cm^2 which was found to be acceptable. Friability was determined to evaluate the ability of the tablets to with stand the abrasion during packing, handling and transporting. All the FDT formulations were evaluated for their percentage friability using Roche friabilator and the results are shown above. The average percentage friability for all the formulations was between 0.17- 0.62 which was found to be within the limit.

Drug content: All formulations were evaluated for drug content according to the procedure described in methodology section and the results were shown above . The assay values for all formulations were found to be in the range of (95.32 -99.76). According to IP standards the tablets must contain not less than 95% and not more than 105% of the stated amount of the drug. Thus, all the FDT formulation comply with the standards given in IP.

***In vitro* Dissolution time:** *In vitro* disintegration studies showed from 5-30 minutes. The F6 formulation showed *in vitro* Dissolution time i.e30 minutes.

***IN VITRO* DRUG RELEASE STUDIES OF EVEROLIMUS**

Table 6: Dissolution data of Everolimus Everolimus Fast disintegrating tablets

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	**0**	0	0	0	0	0
5	25.89	31.49	38.52	**45.11**	38.52	30.29	44.75	53.14	42.15
10	43.52	53.97	56.71	**53.70**	46.20	43.18	52.93	66.26	56.63
15	56.79	62.35	65.34	**68.10**	53.33	55.37	67.37	78.40	69.27
20	67.28	68.76	72.12	**84.25**	65.50	68.65	75.92	85.14	74.76
25	72.92	76.82	89.59	**91.32**	76.32	74.10	86.21	92.31	86.34
30	77.68	86.43	96.27	**98.82**	87.10	78.90	90.60	97.18	87.72

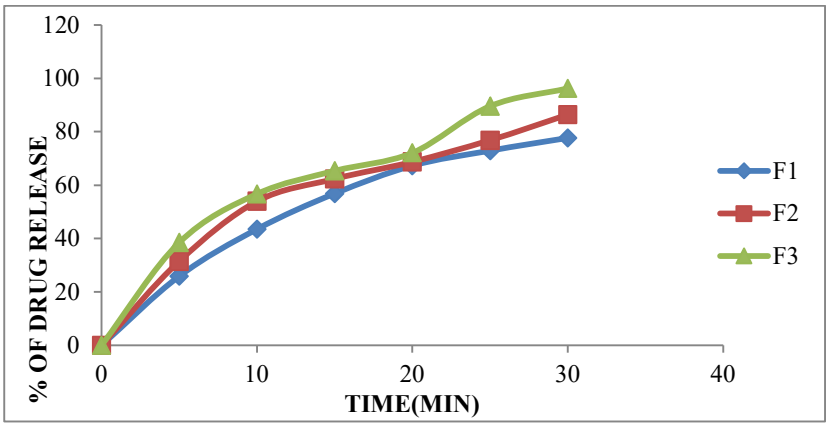

Fig 1: Dissolution profile of formulations F1, F2, F3

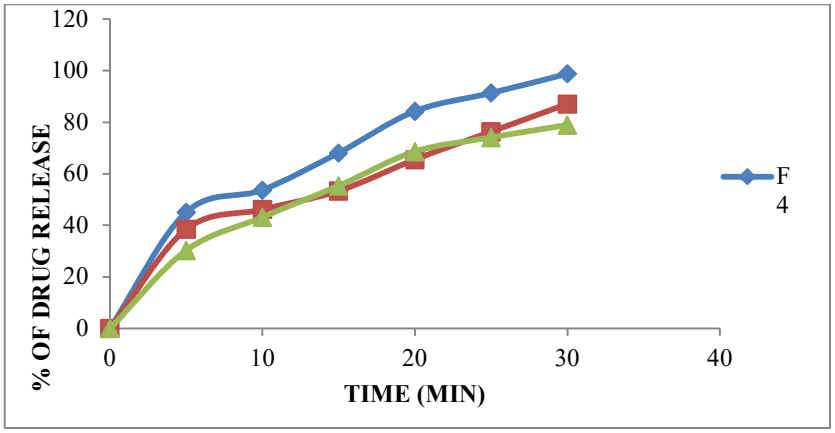

Fig 2: Dissolution profile of formulations F4, F5, F6

CONCLUSION

Fast Dissolving tablets is a promising approach with a view of obtaining faster action of the drug and would be advantageous in comparison to currently available conventional dosage forms. The FDT dosage form had a good balance over disintegration time and mechanical strength. The prime objective of the study was to develop Everolimus Fast Dissolving tablet by using commonly available excipients and conventional technology. From the study, it was concluded that by employing commonly available pharmaceutical excipients such as super disinter grants and swell able excipients and proper filler, a fast disintegrating tablet of Everolimus can be developed which can be commercialized.

ACKNOWLEDGEMENT

We sincerely thank management, visioncollege of pharmaceutical science and research for the encouragement, support & facilities which served as strength to our research work.

REFERENCES

1. Akanksha Sharma, Vishal Garg, Manish Kumar Gupta, Vijay Sharma. Design, Formulation and Evaluation of Fast Disintegrating Tablets of Febuxostat. The Pharmaceutical and Chemical Journal, 2018, 5(1):163-173.
2. Gupta AK, Mittal A, Jha KK. Fast dissolving tablet-A review. The pharma innovation. 2012 Mar 1;1(1):1-8. Available from: https://www.academia.edu/download/74287930/1.pdf
3. Bhaskaran, S., Narmada, G. V., Rapid dissolving tablets a novel dosage form. Indian Pharmacist. 2002, 13(8), 9-12.

4. Birajdar Shivprasad M, Bhusnure Omprakash G, Mulaje Suraj S. Formulation and evaluation of fast disintegrating losartan potassium tablets by formal experimental design. seeds. 2014:5(6);1136-1150. https://www.academia.edu/download/81368815/52.pdf
5. Chang, R.,Guo, X., Burnside, B. A., Couch, R. Fast-dissolving tablets, Pharm. Tech., 2000; 24(6):52-58. Available from: https://elibrary.ru/item.asp?id=6095733
6. Kuchekar, B. S., Arumugam, V., Design of Fast Dissolving Tablet. Indian J. Pharm. Edu., 2001;35(4).150-152.
7. Uppala L, Pranusha P. Development and evaluation of fast disintegrating tablets of ondansetron with natural and synthetic super disintegrating agents. SOJ Pharm Sci. 2015;2(3):1-7. Available from: https://pdfs.semanticscholar.org/89d3/5cc03b46d456c30b830fff865dc7098b4863.pdf
8. Jivraj M, Martini LG, Thomson CM. An overview of the different excipients useful for the direct compression of tablets. Pharmaceutical science & technology today. 2000 Feb 1;3(2):58-63. Available from: https://www.sciencedirect.com/science/article/pii/S1461534799002370
9. Azharuddin M, Kamath DS, Pillai SS, Shabaraya AR. Formulation and evaluation of fast disintegrating tablets of Granisetron HCl using natural polymers. Research in Pharmacy. 2015 Oct 28;1(2). Available from: https://core.ac.uk/download/pdf/236013000.pdf
10. Ratnaparkhi MP, Mohanta GP, Upadhyay L. Review on: Fast dissolving tablet. Journal of pharmacy research. 2009 Jan;2(1):5-12. Available fom: https://citeseerx.ist.psu.edu/document?repid=rep1&type=pdf&doi=4865f017c8fea0548be8a8697ef4bffe1dc7f839
11. Neha T, Mohit T, Neha G, Upendra N. Formulation and evaluation of fas t disintegrating tablets of caffeine by using effervescent formulation approach. Der Pharmacia Lettre. 2012;4(5):1490-4.
12. Pebley WS, Jager NE, Thompson SJ, inventors; Oregon Freeze Dry Inc, assignee. Rapidly distintegrating tablet. United States patent US 5,298,261. 1994 Mar 29. Available from: https://patents.google.com/patent/US5298261A/en
13. Ritika Malik, Brahamdutt, Sandeep Kumar, Nitesh Choudhary, Manjusha, Choudhary, Vikaas Budhwar. Formulation and Evaluation of Fast Disintegrating Tablet of Telmisartan. Inventi Rapid: Pharm Tech, 2017, 8(2): 1-6.
14. Biradar SS, Bhagavati ST, Kuppasad IJ. Fast dissolving drug delivery systems: A brief overview. The internet journal of pharmacology. 2006;4(2):256-60. Available from: https://ispub.com/IJPHARM/4/2/5196
15. Chaudhari P, Meshram P, Chaskar P. Formulation and Evaluation of Fast Disintegrating Tablet of Telmisartan. Inventi Impact: Pharm Tech. 2013 Jul 15.5(2).