Research Article

Design and Development of Polymer Based Fast Disintegrating Wafers of Selective Antihypertensive Agent

Dr. Santosh Payghan[1]*, Dr. Sanjeevani Desai[2], Milind Lade[3], Vaishali Payghan[2]
[1] Principal, Vasantidevi Patil Institute of Pharmacy, Kodoli, Maharashtra, India.
[2] Assistant Professor, Vasantidevi Patil Institute of Pharmacy, Kodoli, Maharashtra, India.
[3]Tatyasaheb Kore College of Pharmacy, Warananagar, India.
***Corresponding author's E-mail:** sanjeevani.desai@yspm.in

Received: 16-06-2022; **Revised:** 23-08-2022; **Accepted:** 30-08-2022; **Published on:** 15-09-2022.

ABSTRACT

The objective of present investigation is to Design and develop the Polymer based fast disintegrating oral wafers of antihypertensive agent by solvent casting method and to study the effect of various Film Formers, Plasticizers and super disintegrants. Polymer based fast disintegrating oral wafers of Amlodipine besylate were prepared by Solvent casting method. Initially different batches were prepared using natural (Pullulan, Sodium alginate) and synthetic polymers (HPMC E5, HPMC E15) using different super disintegrants and evaluated for appearance, disintegration time and folding endurance. The present study consist of nine different formulations were prepared by varying conc. of various super disintegrants (i.e. Croscarmellose sodium, Sodium starch glycolate, Crospovidone (Polyplasdone XL10) and different plasticizers (Polyethylene glycol 400, Triethyl citrate, Dibutyl phthalate). The formulations were prepared by using hydrophilic Polymer (Pullulan). The optimized batch containing Pullulan, Triethtyl citrate and Cross Carmellose was selected. Formulations were evaluated for thickness, folding endurance, disintegration, % drug content, *in vitro* release study and Permeation study. Drug excipients compatibility study and FTIR spectra revealed that, there was no interaction between Amlodipine and excipients. The Pullulan is the biopolymer which showed the excellent film forming capacity and also it produced the wafer with smooth appearance and maximum stability. The Triethyl citrate gives better folding endurance and flexibility than that of PEG 400 and Dibutyl phthalate. The optimized Formulation F4 having concentration of Cross Carmellose sodium 11.25% with excellent film former Pullulan was having in vitro disintegration time below 40 seconds and shows 98.55% Cumulative drug release within 5 min. The F4 batch is stable for 90 days and there was no any significant change in evaluation parameters like appearance, disintegration time, surface pH and % CDR. It was concluded that Amlodipine besylate was successfully formulated in fast disintegrating wafers which were found to be having good mouth feel, faster disintegration and better drug release and stability.

Keywords: Oral Wafers, Solvent casting method, Plasticizer, Super disintegrant.

QUICK RESPONSE CODE →

DOI: 10.47583/ijpsrr.2022.v76i01.007

DOI link: http://dx.doi.org/10.47583/ijpsrr.2022.v76i01.007

INTRODUCTION

Polymer based fast disintegrating wafer is a breakthrough in the era of Fast Dissolving Delivery System (FDDS). The ability of wafers to deliver the drug for systemic action through oral mucosa while avoiding the hepatic metabolism has accelerated research in field of Pharmaceutical Technology.[1-2]

Swallowing of tablet or capsules may become difficult in some cases like motion sickness, allergic attack or coughing and unavailability of water. In order to assist these patients, several fast-dissolving drug delivery systems have been designed and developed. To overcome these difficulties and to provide high patient compliance, scientists have developed new oral fast disintegrating dosage form such as the "Fast Disintegrating Wafer" has been developed which offers the combined advantages of ease of dosing and convenience of dosing in the absence of water. Oral fast disintegrating wafer is a relatively a novel dosage form in which thin wafer is prepared using water soluble polymers, which rapidly disintegrates on tongue or buccal cavity.[3] Oral Fast disintegrating wafer is also known as mouth dissolving films (MDF), oral strips, Oro-dispersible films (ODF).[4-5] On placing mouth dissolving films in the mouth, saliva serves to rapidly dissolve the dosage form. The saliva containing the dissolved or dispersed medicament is then swallowed and the drug is absorbed in the normal way. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach & it may produce rapid onset of action. In such cases bioavailability of drug is significantly greater than those observed from conventional tablets dosage form.[6]

Amlodipine besylate is a long-acting calcium channel blocker used in the cure of chronic stable angina, vasospastic angina and hypertension.[7] Amlodipine is a sparingly soluble orally administered drug and the rate of absorption is frequently controlled by the rate of dissolution. The rate of dissolution can be improved by incorporating the drug in a fast-dissolving dosage form.[8] The simplicity and cost effectiveness of the direct compression process have positioned this technique as an alternate to granulation technologies.[9]

In the present study, we have developed an effective and stable Fast disintegrating Wafer of Amlodipine besylate formulated by solvent casting method with adequate hardness, low disintegration time and pleasant taste.

MATERIALS AND METHODS

Materials

Amlodipine Besylate was supplied by Vergo Pvt.Ltd. Goa. Pullulan, Sodium alginate, HPMC E5, HPMC E3, Cross Povidone, Cross Carmellose, Sodium starch glycolate, Polyethylene Glycol 400, Triethyl citrate, Dibutyl phthalate were provided by Unique Chemicals, Kolhapur as a gift sample. All the solvents and reagents used in the study were of analytical grade.

Formulation and Development

Selection of Drug polymer concentration by Solvent casting method[10]

An appropriate solvent (water) that dissolves the API, polymer and plasticizers was selected. When substances were dissolved after stirring the solution, casting on glass plate was done which results in thin film. Drying of film was performed for 30 min under ambient condition and then in vacuum drying cabinet to ensure fast and complete drying of film. To analyse extent of solubilization capacity of API visual inspection of the film was performed 7 days after open storage.

Table 1: Formulation batches of fast disintegrating wafers based on CCD

Sr. no	Material	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	API	5	5	5	5	5	5	5	5	5
2	Pullulan	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5
3	PEG 400	8	10	8	10.4	9	9	7.59	10	9
4	CCS	3	3	6	4.50	6.6	2.38	4.50	6	4.50
5	Citric acid	2	2	2	2	2	2	2	2	2
6	Aspartame	2	2	2	2	2	2	2	2	2

* All values in table are expressed in %

Formulation and evaluation of Fast Disintegrating Wafers

Formulation design of Fast disintegrating wafer

Response surface central composite design with one central point gives 9 formulation batches as follows with varying super disintegrant concentration and compression force. The batches are shown in table 1.

Physical Evaluation of Fast Disintegrating Wafer: [11-12]

Appearance

Appearance of wafer system was studied by its visual inspection for its morphological characterization.

Thickness

The thickness of wafer was determined by using digital vernier calliper. The readings were recorded in triplicate. The thickness should be optimum because it is directly affecting the disintegration of wafer.

Surface pH

The surface pH of prepared batches was determined by moistening the wafer surface with 0.5 ml saliva buffer pH 6.8.

Disintegration Time

Pharmacopoeia disintegrating test apparatus may be used for this study.

Assay

The Fast disintegrating wafers equivalents to 20 mg Amlodipine besylate dissolved in 20 ml of simulated salivary fluid having pH 6.8. The sample was filtered through 0.45 mm membrane filter and the drug content was determined at 239 nm by UV Spectrophotometer.

In-vitro Dissolution Test

Dissolution testing can be performed using the standard basket or paddle apparatus described in Indian Pharmacopoeia. Salivary Phosphate buffer 6.8 was selected as dissolution medium. Many times, dissolution test can be difficult due to tendency of the strips to float on the dissolution medium where paddle system is used. The amount of drug released was determined at 239 nm by UV Spectrophotometer.

Permeation study through buccal mucosal membrane

Permeation study was carried out by using Franz diffusion cell. The amount of drug permeated was determined at 239 nm by UV Spectrophotometer.

Design of Experiment[13]

Response surface methodology (RSM) is a widely practiced approach in the development and optimization of drug delivery devices. Based on the principle of design of experiments (DOE), the methodology encompasses the use of various types of experimental designs, generation of polynomial equations and mapping of the response over the experimental domain to determine the optimum formulation(s).

Stability Studies [14]

Stability measurement is done by storing the of wafers were stored under controlled conditions 40°C/75% over a period of one months in stability chamber according to the ICH guideline. During storage period various evaluating parameter like thickness, morphological properties, disintegration time, drug content, surface pH and dissolution behaviour are checked.

RESULT AND DISCUSSION

Formulation and Development

Selection of Drug polymer concentration by Solvent casting method

Different polymers like Pullulan, Sodium alginate, HPMC E3, HPMC E5 and HPMC E15 were used for preparation of FDF. All the films were evaluated by considering two parameters i.e., film forming capacity and appearance. The HPMC E series, Pullulan showed the good film forming capacity, so they were selected for the trial batches.

Formulation and evaluation of Fast Disintegrating Wafers

Formulation design of Fast disintegrating wafer

A 3^2 full factorial design was selected, and two factors were evaluated at two levels. The percentage of Cross Carmellose and Triethyl citrate were selected as independent variables and the dependent variables were Disintegration time and folding endurance.

Final Equations for folding Endurance and Disintegration time in terms of coded Factor

Folding Endurance =+105.44+105.44+8.883E-003+17.79

Disintegration Time =+34.33-10.50+2.82

Table 2: Design summary table

Factor	Name	Unit	Type	Low Actual	High Actual	Low Coded	High Coded	Mean
F1	Cross Carmellose	Mg	Numeric	2.38	6.62	**-1**	**1**	4.50
F2	PEG 400	Mg	Numeric	7.59	10.41	**-1**	**1**	9.00

Table 3: Response summary table

Response	Name	Units	Remark	Analysis	Min.	Max.	Mean
Y1	Folding Endurance	Numbers	9	Polynomial	77	128	105.44
Y2	DT	Sec	9	Polynomial	19	50	34.333

DT- Disintegration time

Physical Evaluation of Fast Disintegrating Wafer

Appearance

Appearance of wafer system was studied by its visual inspection it mentioned in table 4.

Thickness

The thicknesses of formulated films were found to be in range of 0.07 to 0.09 ± 0.01 mm. The values were almost uniform in all F1-F9 formulations as mentioned in table 4.

Surface pH

The surface pH values of the formulations are given in table 4. All the polymers resulted in the formulations that have neutral surface pH. The surface pH of the strips was ranging from 6.8 to 7. The neutral values of surface pH of films assured that there will be no irritation to the mucosal lining of the oral cavity.

Table 4: Evaluation results of Factorial Batches of Fast Disintegrating wafers

Batch code	Appearance	Weight of the film (mg)*	Thickness (mm)	Surface pH*
F1	Transparent	36.68±1.84	0.06±0.008	6.67±0.08
F2	Transparent	34.55±1.22	0.06±0.007	6.78±0.08
F3	Transparent	37.10±1.72	0.08±0.007	6.89±0.08
F4	Transparent	39.88±0.95	0.07±0.008	6.97±0.04
F5	Transparent	38.90±1.14	0.08±0.007	6.90±0.09
F6	Transparent	33.65±1.16	0.08±0.008	6.85±0.04
F7	Transparent	34.45±1.86	0.08±0.008	6.80±0.08
F8	Transparent	37.78±1.84	0.08±0.09	6.86±0.08
F9	Transparent	36.78±1.20	0.08±0.009	6.72±0.04

*All values are expressed as mean ± S.D. (n=3)

Disintegration time

The D.T. of wafer was in the range 19-50 seconds. It was observed that as the solid contents of the wafer increased, D.T. also increased. The results are given in table 5.

Assay

Fast disintegrating wafer drug content was determined by UV Visible Spectrophotometer. The results are shown in table 5.

In-Vitro Dissolution Studies

The dissolution medium simulated saliva was used for the dissolution study of optimized F4 formulation.

The cumulative % drug release of F4 formulation indicated the 98.55 % drug release in simulated saliva in 5 min.

Permeation study through buccal mucosal membrane

Permeation study through oral mucosa indicated that the extent of permeation of Amlodipine Besylate from formulation F4 observed 88.28 % 30 min. The results are given in table 7 and fig. 2.

Table 5: Evaluation of Factorial Batches of Fast Disintegrating wafers

Sr. no.	Batch code	Folding endurance	Disintegration Time (sec)	Drug content per film (3×2cm) %
1	F1	87±0.58	42±1.73	98.79±0.80
2	F2	118±1	50±1.73	97.88±0.65
3	F3	92±2	25±1.73	98.36±0.89
4	F4	126 ±1	36±	98.85±0.77
5	F5	118±1.73	19±1	98.73±0.4
6	F6	107±1	48±1.7	98.12±0. 99
7	F7	77±1.73	25±1	97.94±1.92
8	F8	118±1.73	24±1	98.79±0.83
9	F9	109±1.73	42±1.73	98.18±0.83

*All values are expressed as mean ± S.D. (n=3)

Table 6: Dissolution data of factorial batches of Fast disintegrating wafers

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	33.56 ±1.49	34.18 ±1.67	36.18 ±0.63	39.45 ±0.83	29.27 ±1.37	31.27 ±1.14	28.18 ±0.31	31.93 ±0.73	36.18 ±0.83
2	45.81 ±0.55	44.73 ±1.09	47.64 ±1.14	57.27 ±0.55	36.02 ±1.47	56.91 ±1.26	36.02 ±1.47	41.82 ±0.63	58.27 ±1.23
3	58±0.31	53.64 ±0.83	55.82 ±0.83	74.55 ±0.83	46.18 ±1.14	62.91 ±0.83	55.64 ±0.94	53.09 ±1.14	68.55 ±0.83
4	67.09 ±1.89	60.91 ±1.14	67.64 ±1.89	86.73 ±0.94	55.82 ±0.63	72.91 ±1.14	64.00 ±0.83	60.91 ±0.83	77.27 ±0.83
5	78±0.94	74.18 ±1.44	74.91 ±0.83	98.55 ±0.31	65.45 ±0.55	81.64 ±0.63	78.36 ±0.83	74.55 ±0.83	88.73 ±0.31
6	95.09 ±0.31	83.64 ±1.14	82.73 ±0.83	-	73.45 ±0.83	87.82 ±0.55	86.00 ±0.83	83.27 ±0.83	97.82 ±0.83
7	-	96.18 ±0.83	88.18 ±1.92	-	81.27 ±0.55	94.73±0.83	94.18±0.63	88.18±0.31	-
8	-	-	95.45 ±0.94	-	96.73±0.63	-	-	91.82±0.83	-
9	-	-	-	-	-	-	-	97.09 ±1.09	-

*All values are expressed as mean ± S.D. (n=3)

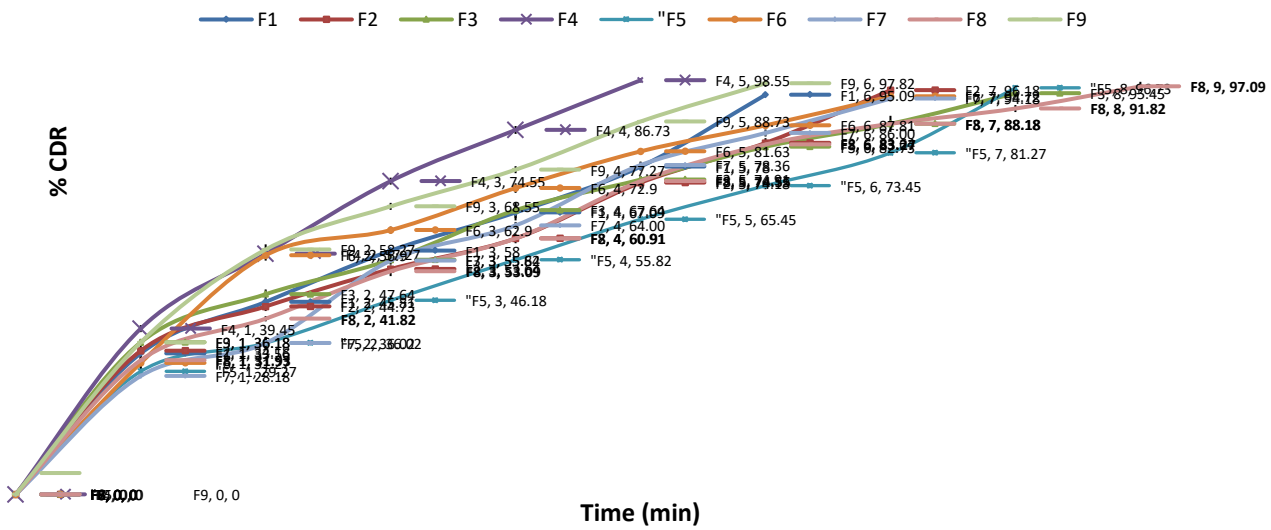

Figure 1: Dissolution data of Optimized formulation in Salivary Phosphate buffer 6.8

Table 7: Permeation study of optimized batches

Sr. no	Time (min.)	% Drug Permeated
1	5	29.56±0.53
2	10	38.27±0.60
3	15	49.64±0.70
4	20	65.38±0.16
5	25	73.27±0.15
6	30	88.28±0.12
7	35	88.24±0.14

*All values are expressed as mean ± S.D. (n=3)

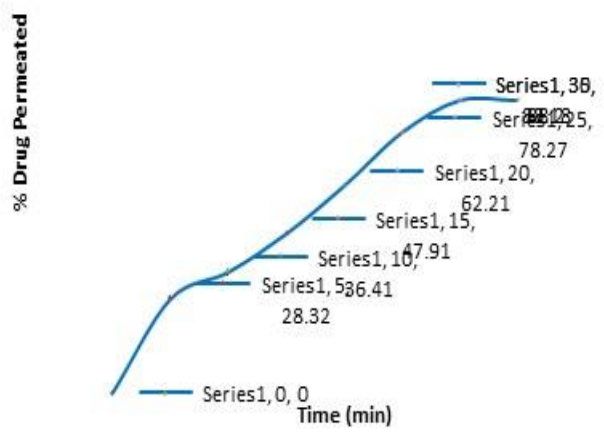

Figure 2: Permeation study of formulation F4

Design of Experiment

Response surface plot for folding endurance

As the concentration of Triethyl citrate from 8mg to 10mg, the increase in folding endurance of wafer system was observed and recorded. So, it was concluded that the plasticizer facilitates wafer folding endurance and increases its flexibility.

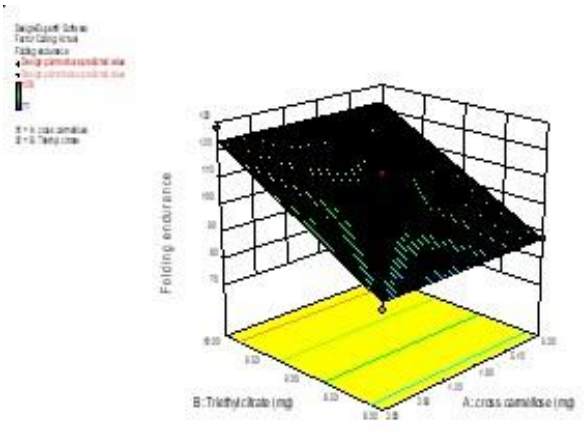

Figure 3: Response surface plot

The Fig. 4 Predicted values vs Actual values plot for folding endurance explained the differential residue present between the predicted values and actual values obtained from results.

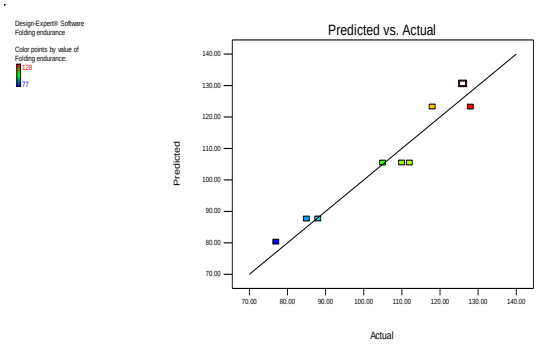

Figure 4: Predicted values vs Actual values plot

Response surface plot for disintegration time

The Disintegration time depends upon the concentration of croscarmellose sodium in wafer system. As the concentration of Cross Carmellose sodium from 3mg to 6mg, the decreased Disintegration time of wafer system was observed and recorded. So, it was concluded that the super disintegrants facilitates wafer disintegration and decrease the Disintegration time. The results are shown in fig. 5.

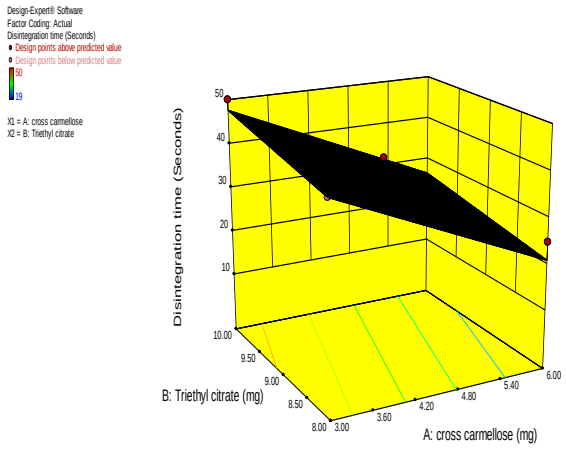

Figure 5: Response surface plot

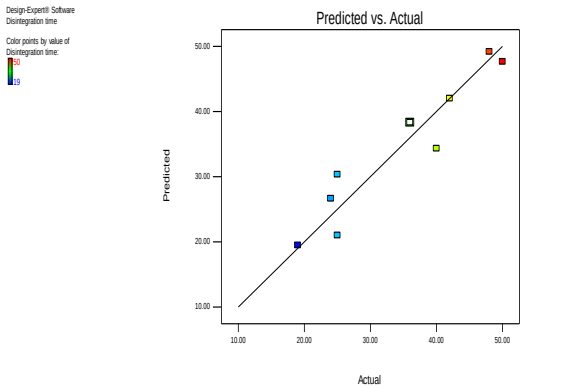

Figure 6: Predicted values vs Actual values plot

The plot of Predicted vs Actual values plot for disintegration time (Fig. 6) concludes that the disintegration time values obtained from optimized

batches are nearer to the predicted value. Thus, obtained values of disintegration time were significant.

Stability studies

The optimized F4 formulation was selected for stability studies on the basis of results of *in vitro* disintegration time, folding endurance and high cumulative % drug release. The results obtained were tabulated in Table 8. From these results it was concluded that, formulations F4 is stable and retained their original properties with minimum differences. The *in vitro* release profile of F4 batch at 40 °C/ 75% RH condition after 90 days shows 94.44 ± 0.89 % CDR as shown in fig. 7 which indicated that there is no or minor alteration of original properties after storage.

Table 8: Stability studies of optimized formulation

Parameters	Initial	After 90 days stability studies
Folding endurance	126 ± 1	126±2
Surface pH	6.8 ± 0.08	6.7 ± 1.73
Disintegration time (sec)	36 ± 1	34±1.73

*All values are expressed as mean ± S.D. (n=3)

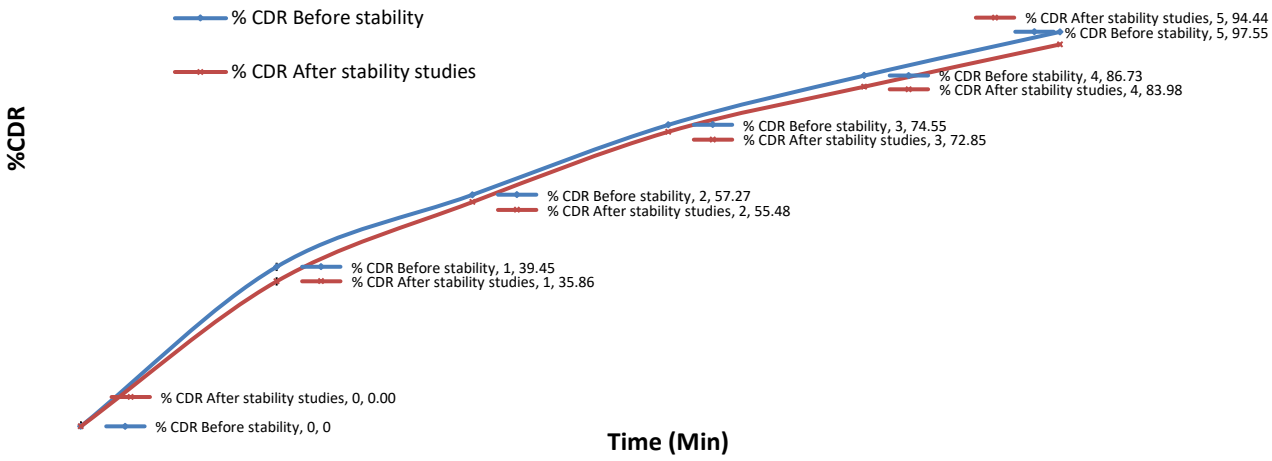

Figure 7: Drug release profile of Batch F4 before and after stability studies

The stability study of fast disintegrating wafers of antihypertensive agent was carried out as per specification. The obtained results show that there were no any significant changes observed in the characteristics of wafer system.

CONCLUSION

For the present study, Amlodipine besylate was selected as a model drug candidate as no marketed wafers of Amlodipine besylate are available in India. The developed Amlodipine besylate wafers disintegrates in oral cavity in less than 40 seconds without the need of drinking water; and improved patient compliance particularly for those who have difficulty in swallowing.

The two variables were studied at two levels thus, a 3^2 full factorial design was applied, and nine different formulations were developed by solvent casting method and evaluated. The wafers prepared using Pullulan, croscarmellose and Triethyl citrate showed the best result among all other wafer formulations. Among 9 optimized batches, Formulation F4 (Pullulan: Triethyl citrate: croscarmellose, 50:25:11) disintegrated in 36 seconds and released 98.55% of drug within 5 minutes and was considered as the best formulation. The Permeation study of F4 batch showed the optimum and acceptable results i.e., 86% of drug was permeated within 30 seconds. The Stability study showed no significant change the physical nature and drug release of F4 formulation.

The future scope of the present study underlines the use of penetration enhancers like mannitol in formulation to achieve better permeation through oral mucosa.

REFERENCES

1. M. Satam, and Y. Pawar, Fast Dissolving Oral Thin Film: A Review, International Journal of Universal Pharmacy and Bio Sciences. 2013; 2(4): 27-39.
2. D. Hitesh, M. Dasharath, R. Ankurkumar and N. Chhaganbhai, A Review on Oral Strip, American Journal of PharmaTech Research. 2012; 2(3): 61-70.
3. P. Wertz, D. Swartzendruber, C. Squier, Regional variation in the structure and permeability of oral mucosa and skin, Advanced Drug Delivery Reviews. 1993; 1–12.
4. G. Basani, V. Subash, S. Guru and R. Madhusudan, Overview on Fast Dissolving Films, International Journal of Pharmacy and Pharmaceutical Sciences. 2010; 2(3): 29-33.
5. M. Lade, S. Payghan, Z. Tamboli and J. Disouza, Polymer Based Wafer Technology: A Review, International Journal of Pharmaceutical & Biological Archives. 2013; 4(6): 1060 – 1074.
6. C. Squier, C. Lesch, Penetration pathways different compounds through epidermis and oral epithelia, Journal of Oral Pathology & Medicine. 1988; 17512–516.

7. Bhardwaj, V., Shukla, V., Goyal, N., Salim, M.D., Sharma P.K. (2010). Formulation and evaluation of fast disintegrating sublingual tablets of amlodipine besylate using different super disintegrants. International Journal of Pharmacy and Pharmaceutical Sciences, 2010; 2(3): 82-89

8. Sarfraz RM, Ahmad M. "Formulation and in-vitro evaluation of novel Atorvastatin - Amlodipine Oro dispersible tablets" IntJ. Bio, Pharm. Allied Sci., 2014; 3(6): 941-951.

9. Mohammed J and Mohammed G. "Preparation and characterization of Oro dispersible tablets of candesartan cilexetil by direct compression method" Int. J. Pharmacy and Pharmaceut. Sci. 2013; 5 (1): 328-333.

10. A. Mahajan, N. Chhabra, G. Aggarwal, Formulation and Characterization of Fast Dissolving Buccal Films: A Review, Scholars Research Library, Der Pharmacia Lettre. 2011; 3(1): 152-65.

11. D. Parmar, B. Patel and A. Patel, Orally fast dissolving films as dominant dosage form for quick release, international journal of pharmaceutical research and bioscience.2012; 1(3): 27- 41.

12. Desai S., Mali R., Disouza J. Quality by Design-based Formulation and Evaluation of Fast Dissolving Tablet of Aspirin, Asian Journal of Pharmaceutics. Jan-Mar 2018; (Suppl).12 (1): S 92-101

13. Desai S, Disouza J, Sable A, Hosmani A. Development of oro dispersible tablet of atorvastatin calcium using hot melt extrusion. Drug Deliv Lett. 2015; 5: 19-30.

Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.