WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.990
Volume 5, Issue 02, 1281-1295. Research Article ISSN 2277– 7105

FORMULATION, EVALUATION AND OPTIMIZATION OF FLASH DISSOLVING ORAL FILM OF AMLODIPINE BESYLATE

Rajendra Ayer*

National Model College for Advance Learning, Tribhuvan University, Kathmandu, Nepal.

Article Received on
13 Dec 2015,

Revised on 03 Jan 2016
Accepted on 23 Jan 2016

***Correspondence for Author**
Rajendra Ayer
National Model College for Advance Learning, Tribhuvan University, Kathmandu, Nepal.

ABSTRACT

The aim of the present study was to formulate, evaluate and optimize flash dissolving oral film of Amlodipine besylate by solvent casting technique. The film was formulated using different ingredients such as film forming polymer, plasticizer, superdisintegrant, sweetening agent and saliva stimulating agent. The film was evaluated for weight variation, thickness, folding endurance, surface pH, content uniformity, disintegration time and In-vitro dissolution. Plackett Burman Design (PBD) with 6 factors and 12 experimental runs was used for screening of the variable such as Hydroxypropyl methyl cellulose (HPMC), Polyethylene glycol (PEG), Crospovidone (CP), Croscarmellose sodium (CCS), Aspartame (ASP) and Citric acid (CA). Among the excipients, Hydroxypropyl methyl cellulose (HPMC), Polyethylene glycol (PEG) and Croscarmellose sodium (CCS) showed significant effect on disintegration of film hence are selected for further optimization. Box Behnken Design (BBD) with 3 factors (Hydroxypropyl methyl cellulose, Polyethylene glycol and Croscarmellose sodium) and 15 experimental runs was employed for optimization of the formulation. For selection of optimal formulation Contour plot, overlaid contour plot, surface plot and response optimizer plot were drawn and analyzed taking dissolution at 5 minute as response. The optimum formulation was selected which contains 30% of Hydroxypropyl methyl cellulose, 10% of Polyethylene glycol and 4.4 % of Croscarmellose sodium. Thus Flash dissolving film of Amlodipine besylate can be formulated using solvent casting technique for the better patient compliance and faster action of the drug.

KEYWORDS: Flash dissolving oral film, Amlodipine besylate, Hydroxypropyl methyl cellulose, Polyethylene glycol, Croscarmellose sodium and Solvent casting

INTRODUCTION

Oral route of drug delivery is becoming the most desirable and preferred method of administration of therapeutic agents for their systemic as well as local effects. Among the oral dosage forms Tablet and capsules are most popular forms.[1] There are various novel techniques discovered for enhancing bioavailability and patient compliance. Recently, fast dissolving drug delivery systems have started gaining popularity and acceptance as new drug delivery systems, because they are easy to administer and lead to better patient compliance. These delivery systems either dissolve or disintegrate in the mouth rapidly, without requiring any water to aid in swallowing. This novel drug delivery system can also be beneficial for meeting the current needs of the industry which are improved solubility/stability, biological half-life and bioavailability enhancement of drugs.[2] Fast dissolving oral films are the most advanced form of oral solid dosage form due to more flexibility and comfort. It improve the efficacy of APIs by dissolving within minute in oral cavity after the contact with less saliva as compared to fast dissolving tablets, without chewing and no need of water for administration. The FDOFs place as an alternative in the market due to the consumer's preference for a fast dissolving product over conventional tablets / capsules.[2] Potential benefits of FDOF are large surface area promotes rapid disintegration and dissolution in the mouth cavity, due to flexible and less fragile nature there is ease in transportation, storage and consumer handling, ease of administration to patients who are mentally ill, disabled or non-cooperative, precision in the administered dose, good mouth feel, rapid absorption, faster action and improved bioavailability, improved patient compliance, enhance product life cycle and good stability. Benefits of FDOFs over fast disintegrating tablets are larger surface area, no friability loss, less expensive processing and packaging, no fear of choking, less excipients, less time consuming, more elegant and economical. Major limitations of this system are low dose loading capacity and limited taste masking options. There is no restriction to incorporate any therapeutic agent but the agents should have lower doses and need a quicker onset of action are most preferable. [3] A typical composition of quick dissolving system contains Drugs, Water soluble polymers, Plasticizers, Surfactants, Flavor, Color and Some saliva stimulating agents. Manufacturing methods includes Solvent casting, Semisolid casting, Hot melt extrusion, Solid dispersion extrusion and Rolling methods.[4] Evaluation of fast dissolving film generally involves Visual inspection, Weight variation, Thickness measurements, Folding endurance test, Surface pH, Disintegration time, Drug content and In-vitro Dissolution Study.[5]

In the present study an attempt was made develop a Flash dissolving oral film of amlodipine besylate for better patient compliance and faster action.

MATERIALS AND METHODS

Materials

Amlodipine besylate and its reference standard were obtained as a gift samples from Lomus Pharmaceutical Private Limited, Gothatar, Bhaktapur, Nepal. Hydroxypropyl methyl cellulose (HPMC), Crospovidone (CP), Croscarmellose sodium (CCS), Polyethylene glycol (PEG), Lactose, Aspartame and Citric acid (CA) were provided by research laboratory of National Model College for Advance Learning, Khusibu, Kathmandu, Nepal. All the other chemicals reagents used were of analytical grades.

METHODS

Analytical method development

Weighed amount of Amlodipine Besylate was dissolved in 0.01N HCL to obtain a 1000mcg/ml solution. This solution was subjected to scanning between 200-400 nm and absorption maximum was determined.

Analytical method validation

UV visible-spectrophotometric method was developed and validated. Method validation was done in terms of Linearity, Specificity, Accuracy and Precision, Limit of Detection (LOD), Limit of Quantification (LOQ) and Range.[6]

Design of Experiment (DOE)

For DOE Minitab 16 software was used. Initially, six excipients such as Hydroxypropyl methyl cellulose, Polyethylene glycol, Croscarmellose sodium, Crospovidone, Aspartame and Citric acid were screened and evaluated for their effects on disintegration time by using Plackett-Burman Design (PBD). Plackett Burman Design with 6 factors results 12 experimental runs. After that, Box Behnken Design (BBD) was used for the statistical optimization of the formulation. Box Behnken Design with 3 factors results 15 experimental runs.

Table 1: Formulation of flash dissolving oral film according to Plackett Burman Design

Formulation Code	Amlodipine Besylate (mg)	HPMC (%)	PEG (%)	CP (%)	CCS (%)	ASP (%)	CA (%)
FP 1	10	40	10	0	4	0	0
FP 2	10	10	10	4	0	3	0
FP 3	10	40	5	4	0	0	0
FP 4	10	10	10	4	4	0	1
FP 5	10	10	10	0	0	0	1
FP 6	10	10	5	0	4	3	1
FP 7	10	40	5	0	0	3	1
FP 8	10	10	5	0	0	0	0
FP 9	10	40	5	4	4	0	1
FP 10	10	10	5	4	4	3	0
FP 11	10	40	10	4	0	3	1
FP 12	10	40	10	0	4	3	0

Table 2: Formulation of flash dissolving oral film according to Box Behnken Design

Formulation Code	Amlodipine Besylate(mg)	HPMC (%)	PEG (%)	CCS (%)	ASP (%)	CA (%)
FB1	10	20	15	4	2	1
FB2	10	40	10	5	2	1
FB3	10	30	15	3	2	1
FB4	10	20	10	3	2	1
FB5	10	40	15	4	2	1
FB6	10	40	10	3	2	1
FB7	10	30	5	5	2	1
FB8	10	40	5	4	2	1
FB9	10	20	5	4	2	1
FB10	10	30	15	5	2	1
FB11	10	30	10	4	2	1
FB12	10	30	10	4	2	1
FB13	10	30	5	3	2	1
FB14	10	20	10	5	2	1
FB15	10	30	10	4	2	1

Formulation of film

Flash dissolving film of amlodipine besylate was prepared by solvent casting technique. Firstly, Film forming polymer (HPMC) was dissolved in distilled water. Then Amlodipine besylate and other ingredients such as Plasticizer (Polyethylene Glycol), sweetening agent (Aspartame), disintegrating agents (Crospovidone and Croscarmellose sodium) and saliva stimulating agent (Citric acid) were dissolved in a little amount of water separately. Sufficient quantity of lactose was also added to make up final volume such that each formulation contains fixed weight and thickness films. The above two solutions were mixed and distilled water was added up to the required volume of 15 ml. Stirring was continued until a

homogenous and bubble free dispersion was obtained. Thus obtained mixture was poured onto a petri dish and was left for drying on a hot air oven overnight at 40°C. The dried films were cut in square shape of desired size of $2cm \times 2cm$ such that each film contains 10 mg of amlodipine besylate and were stored in desicator until further use.[7]

Evaluation of Film

The films were evaluated in terms of Weight variation, Thickness, Folding endurance, Surface pH, Content uniformity, Disintegration time and In-vitro dissolution test.

Weight variation[8]

This test ensures the uniformity of the film formed. Ten films each of 2×2 cm^2 area is cut and weighed individually and compared with the average weight for deviation.

Thickness[9]

Thickness of the film was measured by the help of Micrometer screw gauze.

Folding endurance[3]

The strip of the film was repeatedly folded at a single place until it breaks down. The number of times the strip is folded at the same place prior to breaking gives the value of folding endurance.

Surface pH[10]

The film to be tested was placed in a Petri dish and was moistened with 0.5 ml of distilled water and kept for 30 seconds. The pH was noted after bringing the electrode of the pH meter in contact with the surface of the formulation and allowing equilibration for 1 min. The average of three determinations for each formulation was done.

Drug content[2]

Drug content of all films was determined by UV-Spectrophotometric method. For this 2x2 cm^2 strip was dissolved in 100ml of 0.01 N HCL. The solution was filtered and absorbance was recorded at 239 nm. Drug content was calculated by using standard curve of drug.

Disintegration Time[11]

The disintegration time was measured using modified disintegration method. For this purpose a petri dish was filled with 10 ml of water. The film was carefully put in the center of petri dish. The time for the film to completely disintegrate in to fine particles was noted.

In-vitro Dissolution Study[12]

The release rate Amlodipine besylate from fast dissolving film is determined using United State Pharmacopoeia (USP) dissolution testing apparatus II (paddle method). The dissolution test was performed using 300 ml of pH 6.8 buffer, at 37°C and 50 rpm. A sample (5 ml) of the solution is withdrawn from the dissolution apparatus at regular intervals for 60 min. The samples were replaced with fresh dissolution medium of same quantity. The samples were filtered through a 0.45µ membrane filter. Absorbance of these solutions was measured at 239 nm using a Shimadzu UV/Vis spectrophotometer.

RESULT AND DISCUSSION

Determination of λ max of Amlodipine Besylate in 0.01 N HCL

The λ max of amlodipine besylate in 0.01 N HCL was found to be 239nm.

Analytical Method Validation

The method was found accurate with % recovery of 98.4 %, 99.6% and 101.2% respectively for three different concentrations (7.5 µg/ml, 10 µg/ml and 12.5 µg/ml) which were within the range (98-102) %. The method was also Precise with mean RSD value of 0.135 which was less than 2%. The method was specific for Amlodipine Besylate. The limit of detection of Amlodipine Besylate is 0.338µg/ml. The limit of quantification of Amlodipine Besylate is 1.176µg/ml. The range of concentration detected was found to be 0.338µg/ml to 25µg/ml. The value of correlation coefficient (R^2) was determined to be 0.9998.

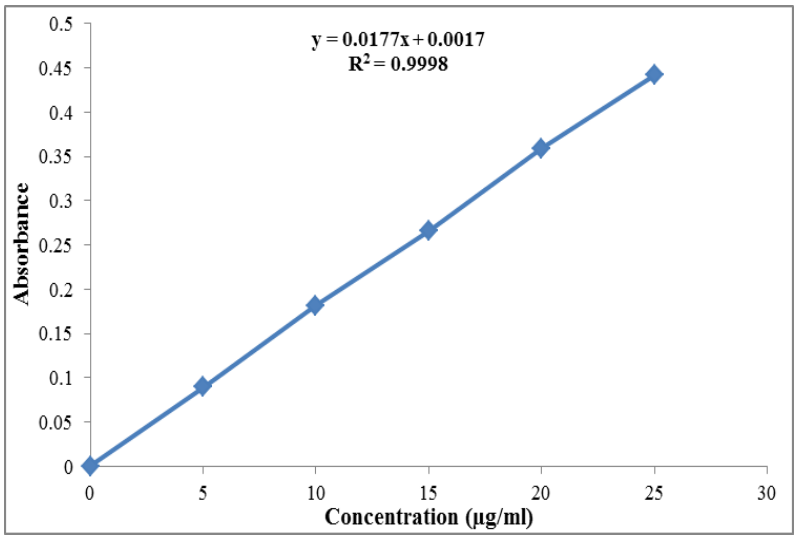

Figure 1: Calibration curve of Amlodipine Besylate reference standard in 0.01 N HCL

Evaluation of Film

Plackett Burman Design

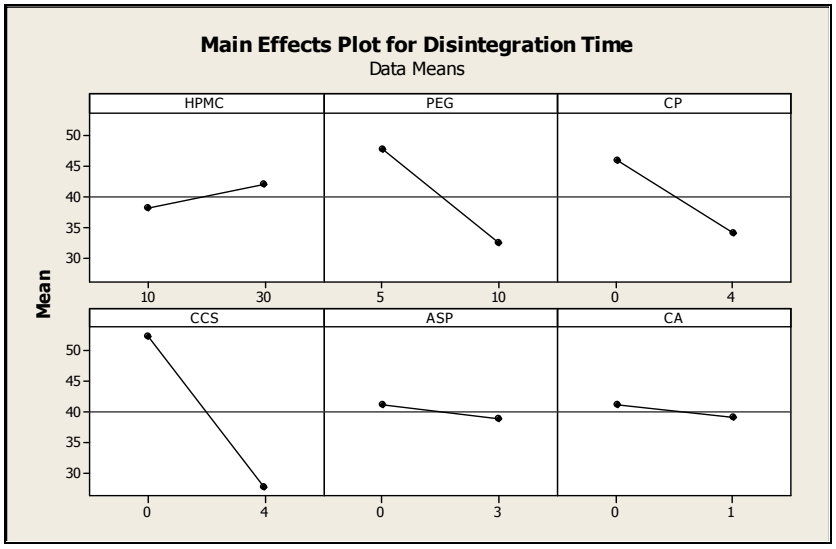

Figure 2: Screening and evaluation of the effects of excipients on disintegration using Plackett Burman Design

Different ingredients generally used in formulation of Flash dissolving films were evaluated for their effects on the disintegration time by the help of Plackett Burman Experimental Design. Altogether six excipients were screened such as Hydroxypropyl methyl cellulose (HPMC), Crospovidone (CP), Croscarmellose sodium (CCS), Polyethylene glycol (PEG), Aspartame (ASP) and Citric acid (CA). The main effect plot for disintegration time of different formulations of PBD showed that ingredients such as Polyethylene glycol, Crospovidone and Croscarmellose sodium has major effects whereas Hydroxypropyl methyl cellulose, aspartame and citric acid has minor effects on disintegration times. After analyzing main effect plot, it was clear that HPMC has positive effect on disintegration of the film i.e, with the increase in the concentration of HPMC in the film the disintegration time of the film increases. Other ingredients such as CCS, CP and PEG has major negative effect on disintegration time i.e, with the increase of their concentration in film the disintegration time decreases significantly. Aspartame and Citric acid has minor negative effect on disintegration time of the film. After comparing the effects of two superdisintegrants viz. Crospovidone and Croscarmellose sodium on disintegration time of film, the Croscarmellose sodium has better effects than the crospovidone. Thus among the two superdisintegrants Croscarmellose sodium has been chosen for further investigation. Three factors viz. Hydroxypropyl methyl cellulose (HPMC), Croscarmellose sodium (CCS) and Polyethylene glycol (PEG) were chosen for further optimization using Box Behnken Design.

Box Behnken Design

During statistical optimization of the formulation using Box Behnken Design 3 Factors viz. Hydroxypropyl methyl cellulose (HPMC), Polyethylene glycol (PEG) and Croscarmellose sodium (CCS) were evaluated for their optimum concentration in the Flash dissolving film formulations. Different plots such as contour plot, overlaid contour plot, surface plot and response optimizer plot were drawn for the evaluations.

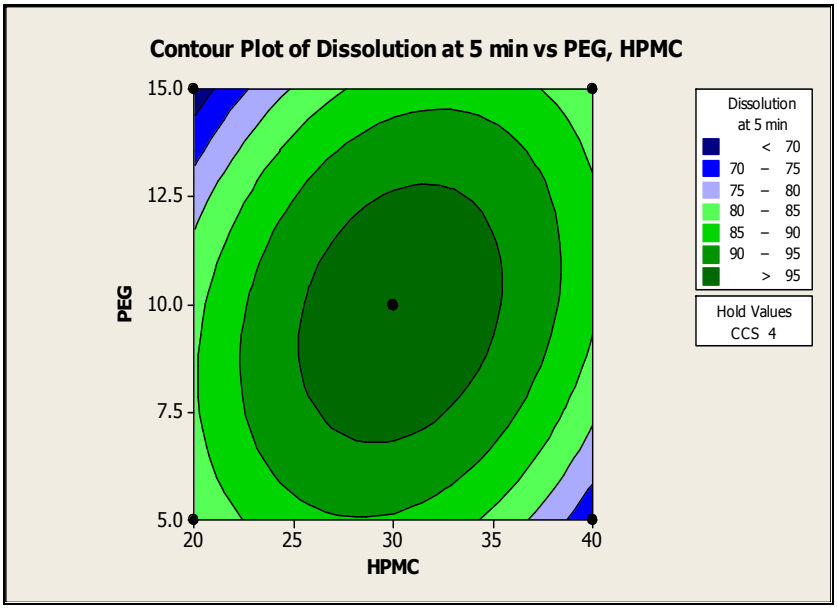

Figure 3: Contour plot of dissolution at 5 minutes vs PEG and HPMC

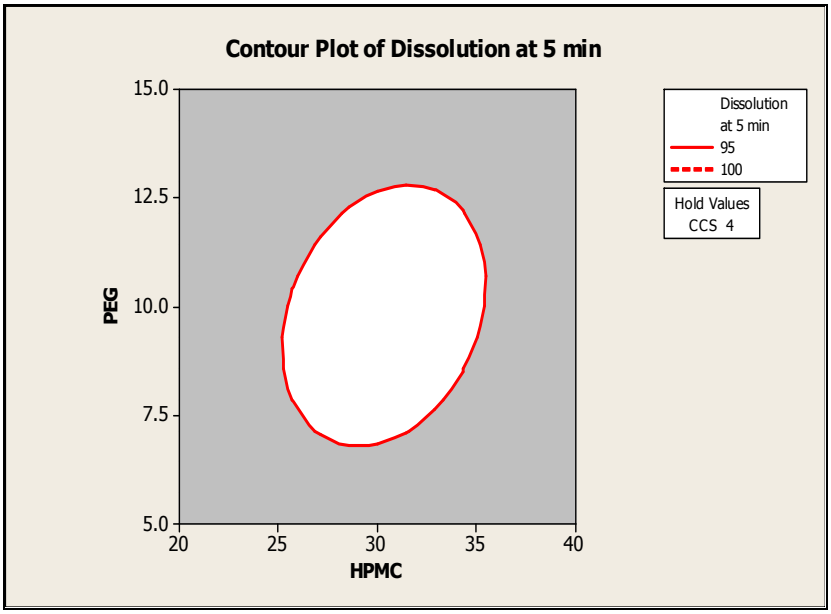

Figure 4: Overlaid contour plot of dissolution at 5 min vs HPMC and PEG

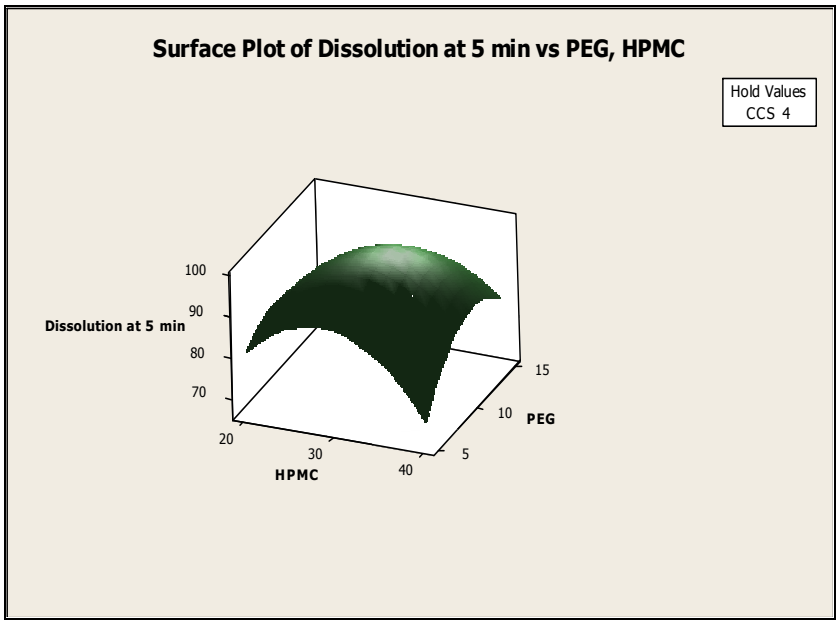

Figure 5: Surface plot of dissolution at 5 min vs HPMC and PEG

The contour plot showed different areas from which we select the concentration of PEG and HPMC in combination for the desired % drug release at 5 minutes. For the release of above 95% of drug in 5 minutes the HPMC should be used in concentration between 25-35% and PEG between 7-12% in combination. The overlaid contour plot of dissolution at 5 minute versus HPMC and PEG showed the area between solid lines from which we can choose the combination of the concentrations of PEG and HPMC which gives above 95% of drug release in 5 minutes. The surface plot of dissolution at 5 minute versus HPMC and PEG showed that the drug release increase upto certain concentration range of HPMC and PEG. The highest drug release was shown at concentrations of 30% of HPMC and 10% of PEG.

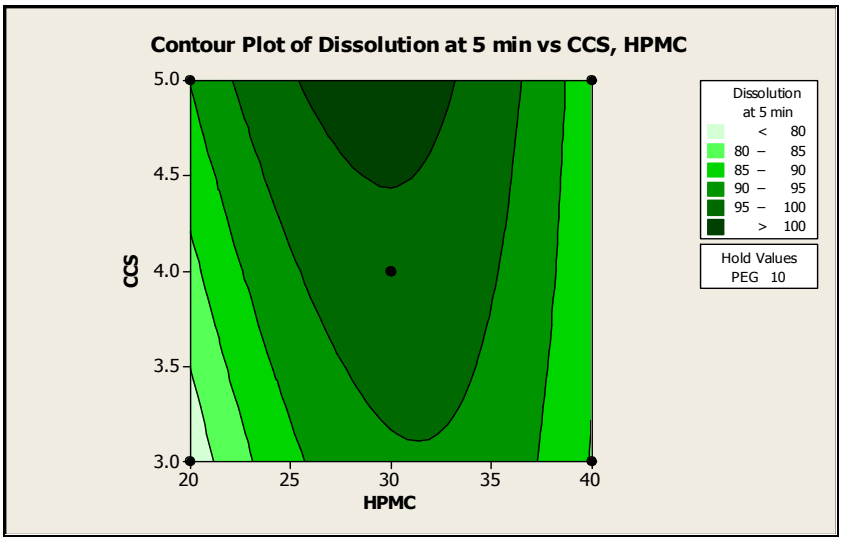

Figure 6: Contour plot of dissolution at 5 minutes vs HPMC and CCS

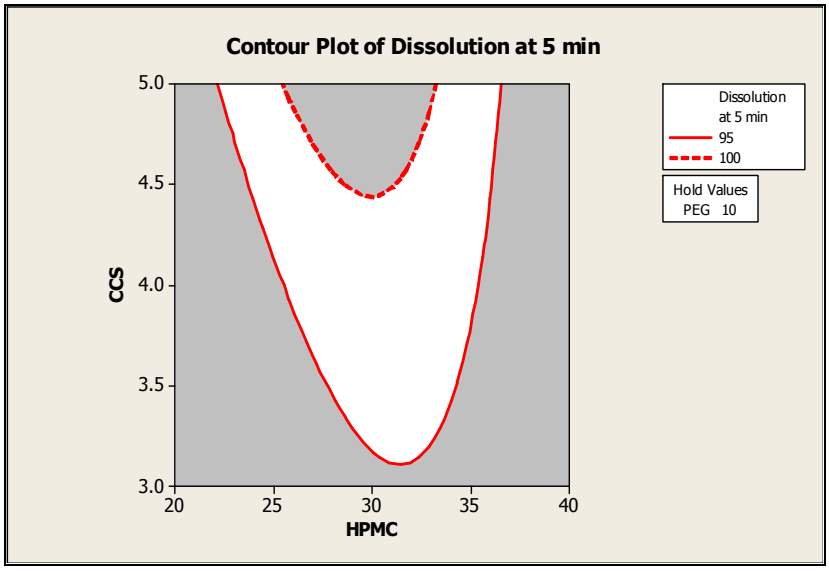

Table 7: Overlaid Contour plot of dissolution at 5 minutes vs HPMC and CCS

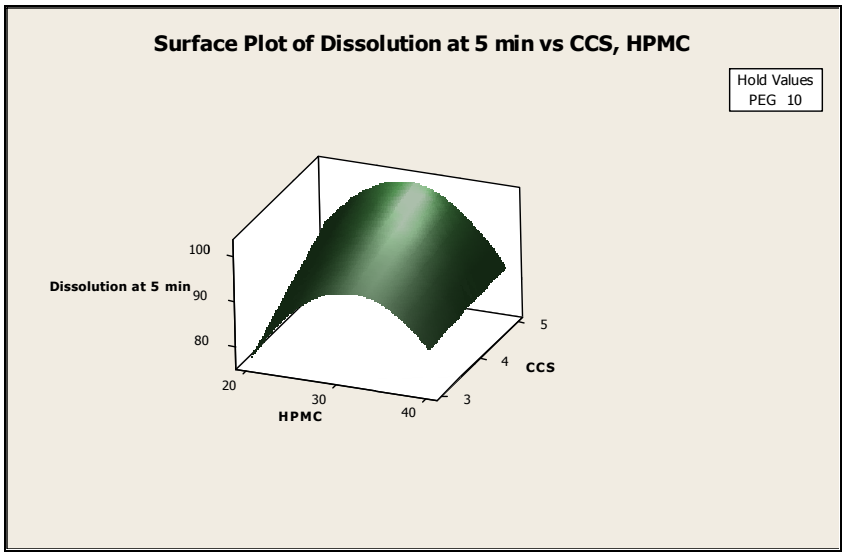

Figure 8: Surface plot of dissolution at 5 minutes vs HPMC and CCS

Contour plot of dissolution at 5 minute vs HPMC and CCS showed different areas for desired % drug release at 5 minutes with different combination of concentrations of HPMC and CCS. For the drug release of above 100% at 5 minutes concentration of HPMC between 27-32% and CCS above 4.5% should be used in combination. The overlaid contour plot of dissolution at 5 minute versus HPMC and CCS also showed the area of concentrations in combination between solid lines and dotted lines which give % drug release between 95-100%.For drug release above 95% the concentration in combination of 23-37% of HPMC and above 3.2% of CCS were required in the film. The surface plot of dissolution at 5 minute versus HPMC and CCS showed that the drug release increase upto certain concentration range of HPMC but for

CCS the drug release is proportional to the concentrations. The highest drug release was shown at concentrations of 30% of HPMC.

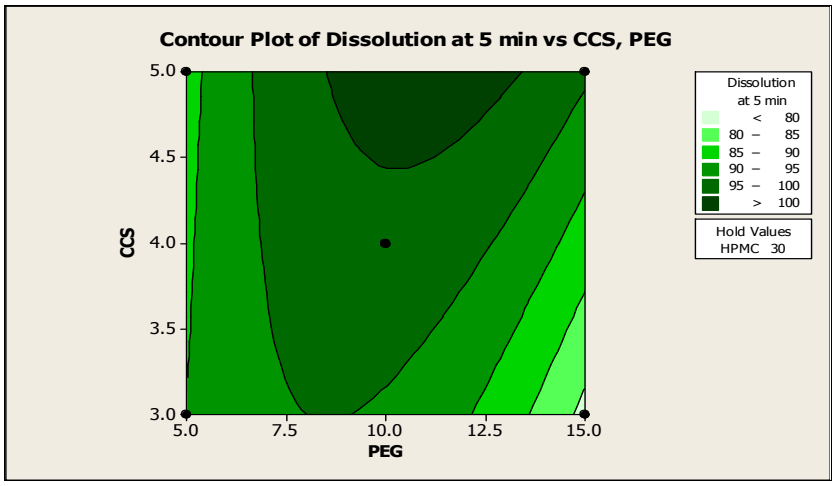

Figure 9: Contour plot of dissolution at 5 minutes vs PEG and CCS

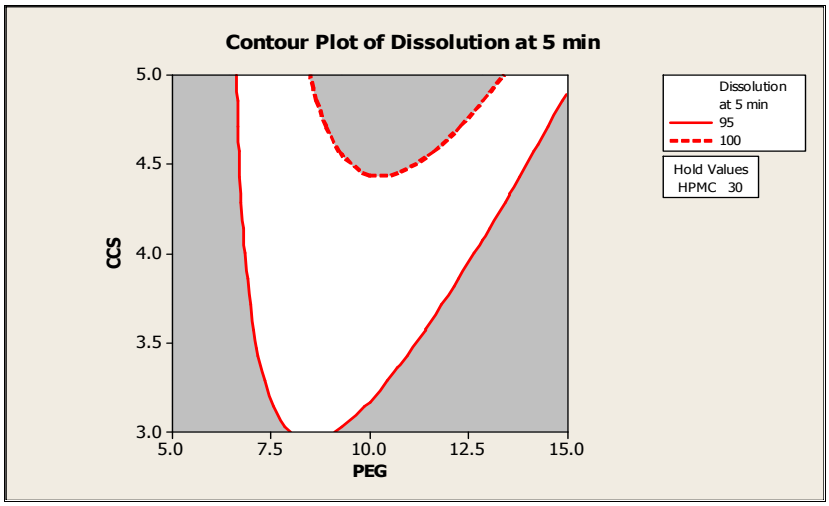

Figure 10: Overlaid Contour plot of dissolution at 5 minutes vs PEG and CCS

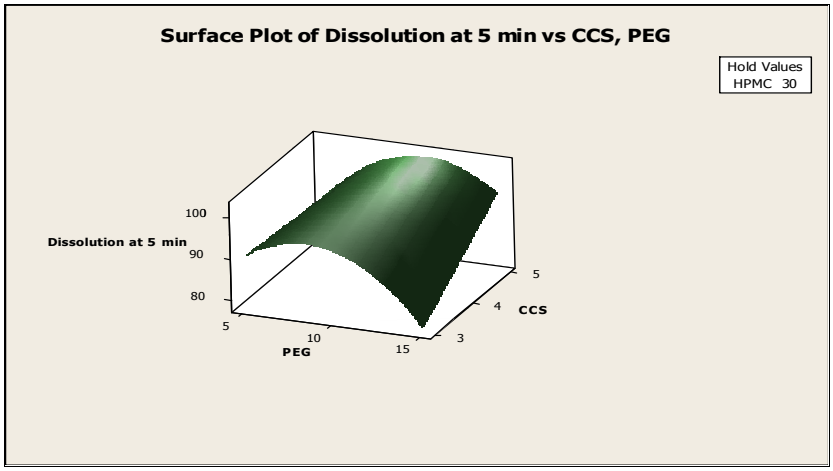

Figure 11: Surface plot of dissolution at 5 minutes vs PEG and CCS

Contour plot of dissolution at 5 minute vs PEG and CCS showed different areas for desired % drug release at 5 minutes with different combination of concentrations of PEG and CCS. For the drug release of above 100% at 5 minutes concentration of PEG between 8.5-12.5% and CCS above 4.5% should be used in combination. The overlaid contour plot of dissolution at 5 minute versus PEG and CCS also showed the area of concentrations in combination between solid lines and dotted lines which give % drug release between 95-100%. The surface plot of dissolution at 5 minute versus PEG and CCS showed that the drug release increase upto certain concentration range of PEG but for CCS the drug release is proportional to the concentrations. The highest drug release was shown at concentrations of about 10% of PEG in the film.

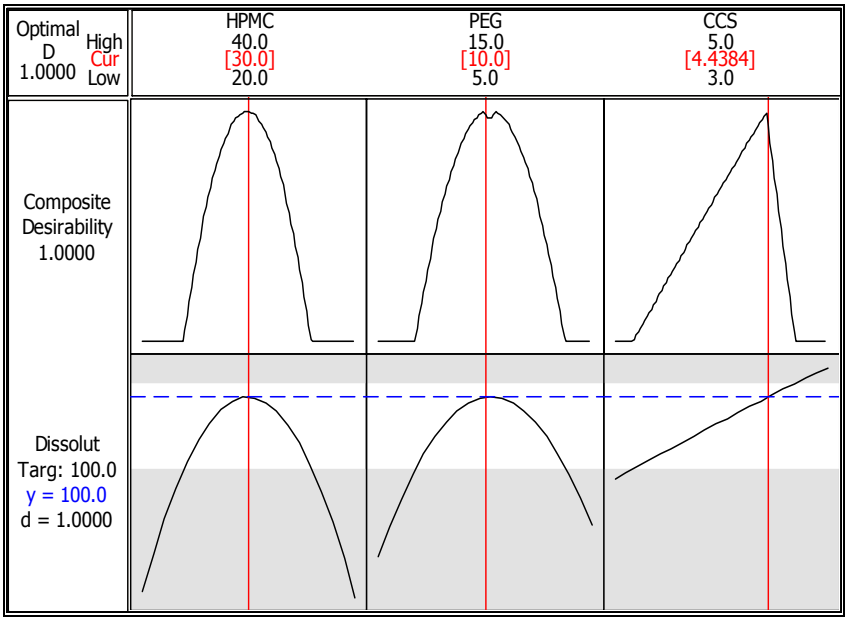

Figure 12: A response optimizer plot for optimization of the formulation according to Box Behnken Design

The response optimizer plot of dissolution at 5 minute with target value of 100% drug release, lower value of 95% drug release and higher limit of 101% of drug release showed that the exact concentrations of three factors viz. HPMC, PEG and CCS in combinations needed were 30% of HPMC, 10% of PEG and 4.4% of CCS.

Thus after analyzing the contour plot, overlaid contour plot, surface plot and response optimizer plot of dissolution at 5 minute versus HPMC,PEG and CCS, the optimum formulation was selected which contains 30% HPMC, 10% PEG and 4.4% of CCS in the flash dissolving film.

Physiochemical properties of the film

Table 3: Physiochemical properties of flash dissolving film prepared according to BBD

Formulation Code	Weight variation (Mean±S.D)	Thickness (Mean±S.D)	Folding endurance	Surface pH	Drug content (%)
FB1	0.84±0.012	0.211±0.011	270	6.6	101.11
FB2	0.82±0.001	0.212±0.003	268	7.2	102.01
FB3	0.83±0.014	0.218±0.012	274	7.1	98.76
FB4	0.78±0.02	0.208±0.017	276	7.3	97.23
FB5	0.82±0.002	0.217±0.022	268	6.9	100.11
FB6	0.79±0.021	0.204±0.027	272	7.1	102.22
FB7	0.81±0.011	0.221±0.012	274	7.3	99.98
FB8	0.78±0.014	0.207±0.032	244	7.1	98.97
FB9	0.80±0.008	0.213±0.004	201	6.8	101.01
FB10	0.81±0.011	0.218±0.026	196	7.3	100.89
FB11	0.82±0.017	0.216±0.015	192	7.1	97.98
FB12	0.81±0.021	0.210±0.017	214	7.0	100.07
FB13	0.83±0.013	0.217±0.018	251	7.3	99.47
FB14	0.82±0.011	0.214±0.007	247	7.2	98.72
FB15	0.78±0.019	0.212±0.025	235	6.8	97.77

Disintegration Time

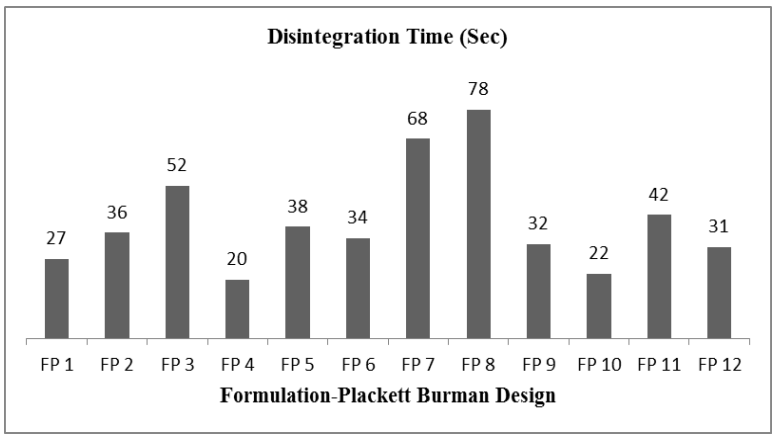

Figure 13: Disintegration time of flash dissolving film batches according to Plackett Burman Design

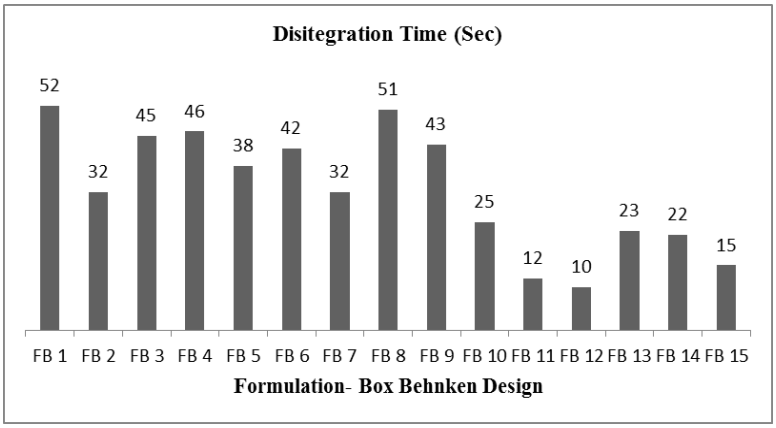

Figure 14: Disintegration time of the flash dissolving film batches according to Box Behnken Design

IN-VITRO DISSOLUTION

Table 4: Percentage drug release from films at different time interval

	% Release of drug at different time interval				
Formulation Code	**2 Min**	**5 Min**	**10 Min**	**15 Min**	**30 Min**
FB1	55.51	68.12	85.50	98.20	100.13
FB2	75.22	87.11	98.70	101.21	101.84
FB3	62.40	78.10	87.20	97.51	100.80
FB4	60.11	76.01	85.42	96.88	101.77
FB5	72.11	85.02	96.10	99.98	102.11
FB6	68.12	81.72	92.45	99.82	101.16
FB7	77.75	89.52	98.88	101.11	102.23
FB8	56.01	70.10	82.52	95.88	99.92
FB9	63.92	76.21	88.21	98.99	100.02
FB10	81.03	91.59	98.87	101.11	102.01
FB11	87.22	98.5	100.07	100.78	100.98
FB12	89.23	99.45	101.01	101.89	101.96
FB13	86.41	95.43	97.92	102.02	102.78
FB14	84.67	94.11	95.77	100.79	101.32
FB15	88.98	98.5	100.67	101.11	101.23

CONCLUSION

This study showed that there was significant effect of the film forming polymer (HPMC), Plasticizer (PEG) and Superdisintegrant (CCS) on the characteristics and integrity of the film. Among different ingredient used HPMC and PEG showed better disintegration and dissolution rate at certain concentration ranges whereas CCS have shown proportional relation. The optimized formulation was selected which contains 30% of HPMC, 10% of PEG and 4.4% of CCS. Thus it can be concluded that flash dissolving film can be formulated using film forming polymer, plasticizer and superdisintegrant by solvent casting technique for better patient compliance and faster action of drug.

ACKNOWLEDGEMENTS

The author is thankful to Department of Pharmacy, National Model College for Advance Learning for providing its support and necessary materials to conduct this research. I am also very thankful to Lomus Pharmaceutical Private Limited for providing Amlodipine besylate as a gift samples which was necessary to carry out this work.

REFERENCES

1. Kunte, S., & Tandale, P. Fast dissolving strips: A novel approach for the delivery of verapamil. Journal of pharmacy and bioallied sciences, 2010; 2(4): 325.

2. Shelke, P. V., Dumbare, A. S., Gadhave, M. V., Jadhav, S. L., Sonawane, A. A., & Gaikwad, D. D. Formulation and evaluation of rapidly dis integrating film of amlodipine besylate. Journal of Drug Delivery and Therapeutics, 2012; 2(2).
3. Panda, B. P., Dey, N. S., & Rao, M. E. B. Development of innovative orally fast disintegrating film dosage forms: a review. Int J Pharm Sci Nanotech, 2012; 5(2); 1666-1674.
4. Arya, A., Chandra, A., Sharma, V., & Pathak, K. Fast dissolving oral films: an innovative drug delivery system and dosage form. International Journal of Chem Tech Research, 2010; 2(1); 576-583.
5. Sabar, M. H. Formulation and in vitro evaluation of fast dissolving film containing amlodipine besylate solid dispersion. International Journal of Pharmacy and Pharmaceutical Sciences, 2013; 5(4); 419-428.
6. Guideline, I.H.T., Validation of analytical procedures: Text and Methodology. Q2 (R1), 2005. 1.
7. Mishra, R., & Amin, A. Formulation development of taste-masked rapidly dissolving films of cetirizine hydrochloride. Pharmaceutical technology, 2009; 33(2); 48-56.
8. Desu, P. K., Brahmaiah, B., Nagalakshmi, A., Neelima, K., Nama, S., & Baburao, C. An overview on rapid dissolving films. Asian Journal of Pharmaceutical Research, 2013; 3(1): 15-23.
9. Thakur, N., Bansal, M., Sharma, N., Yadav, G., & Khare, P. Overview "A novel approach of fast dissolving films and their patients".Advances in Biological Research, 2013; 7(2): 50-58.
10. Prabhu, P., Malli, R., Koland, M., Vijaynarayana, K., D'Souza, U., Harish, N. M., & Charyulu, R. N. Formulation and evaluation of fast dissolving films of levocitirizine di hydrochloride. International journal of pharmaceutical investigation, 2011; 1(2); 99.
11. Borsadia, S., O'Halloran, D., & Osborne, J. L. Quick dissolving films-A novel approach to drug delivery. Drug delivery technology, 2003; 3(3): 63-66.
12. Redddy G.A, Balaji, Naveen KJ, Rajesh BS, Chowdary Y.A. Formulation and evaluation of oral fast disintegrating tablets by using amlodipine besylate solid dispersion by direct compression method. Der Pharmacia Lettre, 2012; 4(2): 683-694.