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Original Research Paper

FORMULATION AND EVALUATION OF TIME DELAYED RELEASE TABLET OF CARVEDILOL PHOSPHATE

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ABSTRACT

The purpose of this study was to evaluate the potential for time delayed release drug delivery system of carvedilol phosphate. Carvedilol phosphate chosen as model drug with an aim to release drug at early morning occurrence of disease can be avoided. Direct compression method was used for preparation of tablets. The prepare tablets were evaluated for various parameters like hardness, thickness, average weight, drug content, % cumulative drug release. The optimized formulation F2 was subjected to stability study for 1 month. In preliminary batches 3 polymers were used in combinations, from the obtained evaluation data of preliminary batches polymers (PHPMC AS HG & EUDRAGIT S 100) were selected for further factorial design batches, from the evaluation parameter data, it had been seen that the average weight of the prepared tablets were in the range of from 78 to 82 mg. Tablets of all batches complied with the mass variation requirement of Indian Pharmacopoeia and no batch varied more than 5% of the average weight indicating consistency in the preparation of the tablet with minimal batch to batch variation. The drug content analysis show that there was accurate distribution of the drug in the tablets and well within the range of 95.95 -102.39 % of the total amount of the drug added in tablets. It was concluded that formulation of carvedilol phosphate had potential application as anti-hypertension for time delayed delivery of drug following in oral administration.

Keywords: Time delayed release drug delivery system, Carvedilol phosphate, Antihypertensive drug, Extended release tablet.

INTRODUCTION

Oral drug administration has been the predominant route for drug delivery, approx 50% of the drug delivery systems present in the market are ODDS (oral drug delivery systems). Dugs with oral delivery, less risk of damage at the site of administration and does not produce sterility problem.[1,2,3,4] To achieve and maintain required therapeutic blood levels of drug, it can release their drug at pre-determined rate, in controlled manner, duration and location in the body.[5] A Delayed Release dosage form is designed to release the drug at a time other than promptly after administration. Dosage forms can be designed to modify the release of the drug over a given time or after the dosage form reaches the required location. Delayed Release oral dosage forms can control where the drug is released, e.g. when the dosage form reaches the small intestine (enteric-coated dosage forms) or the colon (colon-specific dosage forms). Drug release after a predetermined time in a predetermined location according to delayed Release systems, i.e. after ingestion, they can't release drug immediately, for example pulsatile release capsules, enteric-coated tablets. To provide spatial placement or temporal targeted delivery of a drug to the distal human gut, delayed Release dosage forms are designed. To target tissue over a specified period

of time, spatial placement relates to targeting a drug to a specific organ or tissue, while temporal delivery refers to desired rate of drug release.[6,7] Drugs that are destroyed in gastric fluids, or cause gastric irritation or absorbed preferentially in the intestine, delayed release dosage form is the more effective formulations which are used for it. Such preparations contain a separating layer and enteric coating layer, an alkaline core material comprising the active substance.[8] Several advantages od these systems are reduction in frequency of intakes, reduce side effects, uniform release of drug over time, better patient compliance, improvement in treatment efficacy, ability to improve give special effects, body site can be targated.

Carvedilol is beta adrenergic receptor blocker having ability to decreases systemic vascular resistance via its alpha adrenergic receptor blocking properties, decrease heart rate, myocardial oxygen demand and myocardial contractility. Carvedilol phosphate is racemic mixture in which non-selective beta adrenergic receptor blocker potency is present in enantiomer S (-) and alpha adrenergic blocker potency is present equally in both S (-) and R (+) enantiomers. Carvedilol phosphate and its metabolite BM-910228 (a less potent beta blocker, but more potent antioxidant) have been shown to restore the inotropic responsiveness to Ca2+ in OH- free radical-treated myocardium. Carvedilol phosphate and its metabolites also prevent OH- radical-induced decrease in sarcoplasmic reticulum Ca2+-ATPase activity. Therefore, carvedilol phosphate and its metabolites are beneficial in chronic heart failure by preventing free radical damage.[9,10,11]

MATERIALS AND METHODS

Materials

Materials used in present investigation were Carvedilol phosphate (Torrent Pharma, Ahmedabad, India), HPMC AS HG (Ashland India limited, Kondapur, Hyderabad), Poloxamer 188 (BASF, India), Eudragit S 100 (Evonik India Pvt Limited.), Microcrystalline Cellulose (FML Biopolymer India), Talc and Magnesium stearate (Signet Chemical Corporation, Mumbai, Maharashtra).

Preparation of Floating Tablets

Tablets are prepared by direct compression technique. Carvedilol phosphate was mixed with different excipient according to formulation. This blend of powder was lubricated with the mg-stearate and compressed it by using single punch tablet machine. The MCC was used as water soluble filler for maintaining constant weight of tablet as well as counter balancing the drugs which having poor water solubility. The tablets were compressed to obtain hardness in a range of 4-6 kg/cm^2.

Solubility Enhancement Techniques of Cefpodoxime Proxetil

Carvedilol phosphate is class II drug, so need to enhance solubility. We have used solid dispersion techniques to enhance solubility using Solid dispersion. Poloxamer used as carrier for solid dispersion with different ratio of drug : poloxamer like 1:0.5, 1:1, 1:2.

Evaluation of Prepared Tablets

a) Thickness

Tablet thickness was measured using vernier caliper. Ii is expressed in millimeter.[12]

b) Hardness

The hardness of core tablets was measured using Monsanto Pfizer.[12]

c) Friability

6.8 gm weighed and placed in a Roche friabilator and rotated at 25 rpm for 4 min. The tablets were taken out, dedusted, and reweighed.[12]

The percentage friability of the tablets was calculated using the equation:

$\% F = \{1-(Wt/W)\} \times 100$

Where, % F is friability in percentage, W is the initial weight of tablet and Wt is the final weight of tablets after revolutions. Values of friability of 1 % are considered as an acceptable.

d) In Vitro Drug Release Study

In vitro release study of carvedilol phosphate were evaluated using a USP dissolution testing apparatus type 2 (paddle method) at 37±0.5 °C with rotation speed of 50 rpm in 900 ml of 7.4

phosphate buffer for 8 hr. From this, 5 ml of the dissolution medium were withdrawn at regular time intervals, replaced with an equal volume of fresh dissolution fluid then analyzed for the drug content using UV-Vis spectrophotometer at 332 nm.[52]

e) Drug Content

Equivalent to 80 mg of carvedilol phosphate was taken and transferred to 100 ml volumetric flask, dissolved and diluted with pH buffer. The absorbance of the resulting solution was measured at the λmax of 332 nm using a UV spectrophotometer after filtration through whatmann filter paper. The drug content was calculated using the following equation:

% Drug content (%) = Conc. (µg / ml × Dilution factor × 100 /50

f) Weight Variation

20 tablets from each formulation were randomly picked up and weighed individually and the average weight was calculated. The individual weights were then compared with the average weight.[12]

% Deviation = Avg. weight of tablet–Individual tablet weight/Avg. weight of tablet×100

h) Stability Study

To determine the change in performance of dosage form on storage, stability study was carried out for 1 month at 40° C in a humidity jar having 75% RH according to ICH.[14]

RESULTS

1) Druzg-Excipient Compatibility Study

Analysis of drug and drug with excipients of all were done on Infra-Red (IR) spectroscopy. It was found that all the prominent functional group picks [C=O stretching (1711), Aromatic C-C stretching (1440), Aromatic amines CN stretching (1247), C-O stretching (1005), Carboxylic acid O-H bend (947), C-Cl stretching 828] were observed in physical mixture. According to this, confirmed that no interaction between drug and excipients or incompatibility between drug and excipients.

2) Physico Chemical Characterization of Prepared Tablets

Shown in Table 2 (below).

3) In Vitro Release Study

Shown in Table 3 (below).

4) Stability Study

The tablets were stored for 1 month at 40˚C/ 75% RH. The result do not show any significant change in physical appearance, buoyancy and dissolution behavior of floating tablets in comparison with initial values. Similarity factor f2 was found to be 95%.

DISCUSSION

The angle of repose was found to be in the range of 20.21 to 27.24 having excellent or good flow property. Hausner's ratio of preliminary trials were found to be in the range of 1.21 to 1.33 having moderate flow property. Carr's index were found to be in the range of 16.67 to 25 having passable flow property. The thickness all tablets was found to be in the range of 2.18 to 2.30mm. Sufficient strength of all tablets was also evident since the friability was less than 1%, indicating compliance with the requirements of Indian pharmacopeia. Hardness of tablets were found to be between 7.83 to 7.90 K Pascal indicated good strength. The average weight of the prepared tablets were in the range of from 78 to 82 mg. Tablets of all batches complied with the mass variation requirement of Indian Pharmacopoeia and no batch varied more than 5% of the average weight indicating consistency in the preparation of the tablet with minimal batch to batch variation. The drug content analysis show that there was accurate distribution of the drug in the floating matrix tablets and well within the range of 95.95 -102.39 % of the total amount of the drug added in tablets and therefore comply with the pharmacopoeial limits. The release of the drug was found to be dependent on the amount of HPMC AS HG and EUDRAGIT S 100. According to standard requirement of dissolution, drug release in 1.2 HCL buffer should be less than 10%, drug release in 4.5 acetate buffer should be less than 15% and release of drug in 7.4 phosphate buffer should be less than 75%. As per aim of formulation we have targeted small intestine where pH is around 7. So we have taken

1.2 pH, 4.5 pH and 7.4 pH for small intestine. Based on that, decided limits. Optimization of tablet formulation using 3^2 factorial design was carried out. There were two response considered in factorial design, dissolution at 7 hr and dissolution at 9 hr. Analysis of variance carried out for this 2 responses. Linear model selected for response 1 and linear model selected for response 2. Contour graph and 3D surface graph of these two responses created after choosing model. Optimized batch (F2) find out using software design expert 10. Stability study of optimized batch (F2) was carried out at 40Ċ in a humidity jar having 75% RH specified by ICH. Results of the stability studies showed that there were no significant changes in the drug content and physical appearance of tablets.

CONCLUSION

Cardiovascular disease like heart failure, hypertension etc. mostly occurs at early morning at around 4.00 am to 5.00 am. So if prepare such a drug delivery system which can be taken by patient at bed time and release drug at early morning occurrence of disease can be avoided.So this work mainly focused on solubility enhancement of drug with delayed release tablet of carvedilol phosphate.

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Table 1: Formulation chart of each Cefpodoxime proxetil floating tablet

Batches	Drug (mg)	Eudragit S 100 (mg)	HPMC ASHG (mg)	MCC 102 (mg)	Talc (mg)	Mg. stearate (mg)	Total (mg)
F-1	20	15	15	28.4	0.8	0.8	80
F-2	20	15	20	23.4	0.8	0.8	80
F-3	20	15	25	18.4	0.8	0.8	80
F-4	20	20	15	23.4	0.8	0.8	80
F-5	20	20	20	18.4	0.8	0.8	80
F-6	20	20	25	13.4	0.8	0.8	80
F-7	20	25	15	18.4	0.8	0.8	80
F-8	20	25	20	13.4	0.8	0.8	80
F-9	20	25	25	8.4	0.8	0.8	80

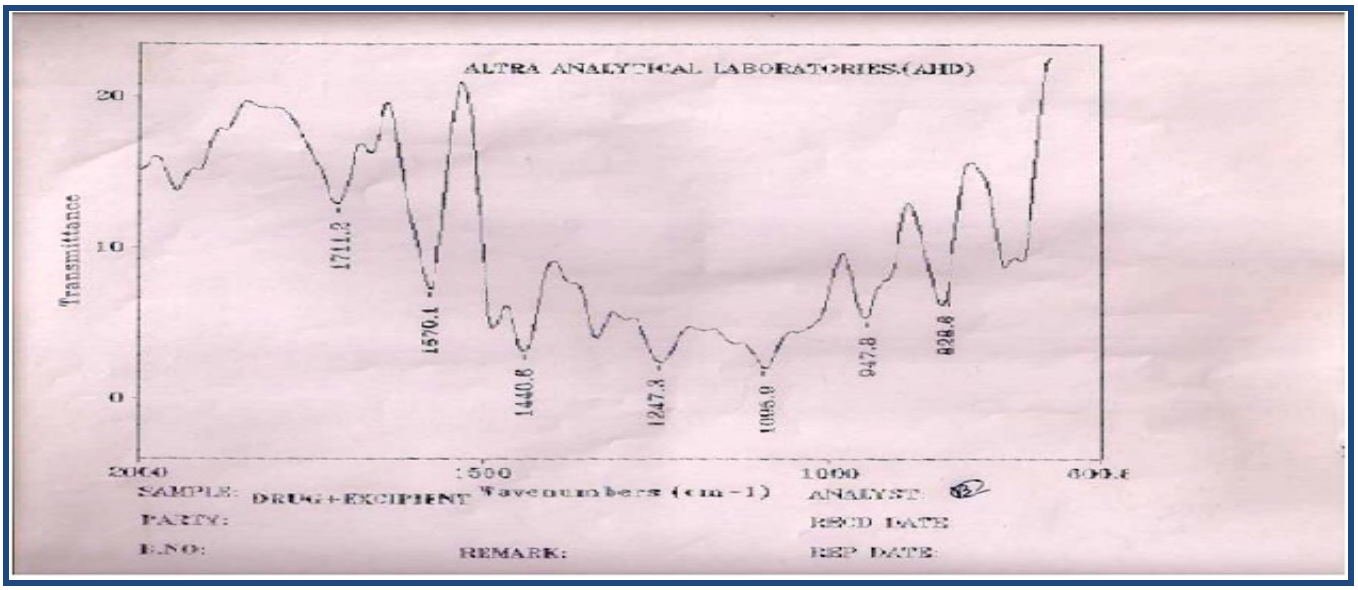

Figure 1: IR spectrum of Drug + Excipients

Table 2: Physico-chemical characterization of Carvedilol phosphate tablet

Batch code	Hardness (KPascal)	Friability (%)	Thickness (mm)	Weight variation (mg)	Drug content (%)
F-1	5.83±0.06	0.22±0.03	2.20±0.15	80±0.3	98.95±0.72
F-2	5.83±0.06	0.26±0.06	2.18±0..12	82±0.4	99.21±0.62
F-3	5.86±0.06	0.25±0.05	2.20±0.31	79±0.2	98.46±0.88
F-4	5.97±0.1	0.20±0.04	2.30±0.31	81±0.3	102.39±0.69
F-5	5.86±0.05	0.26±0.07	2.20±0.21	79±0.2	100.65±0.77
F-6	5.86±0.05	0.30±0.04	2.18±0.15	81±0.3	98.20±0.73
F-7	5.96±0.04	0.26±0.05	2.22±0.37	82±0.5	99.47±0.79
F-8	5.50±0.06	0.35±0.07	2.20±0.25	77±0.4	96.53±0.68
F-9	5.60±0.05	0.25±0.02	2.20±0.31	82±0.3	102.34±0.62

(*n = 3)

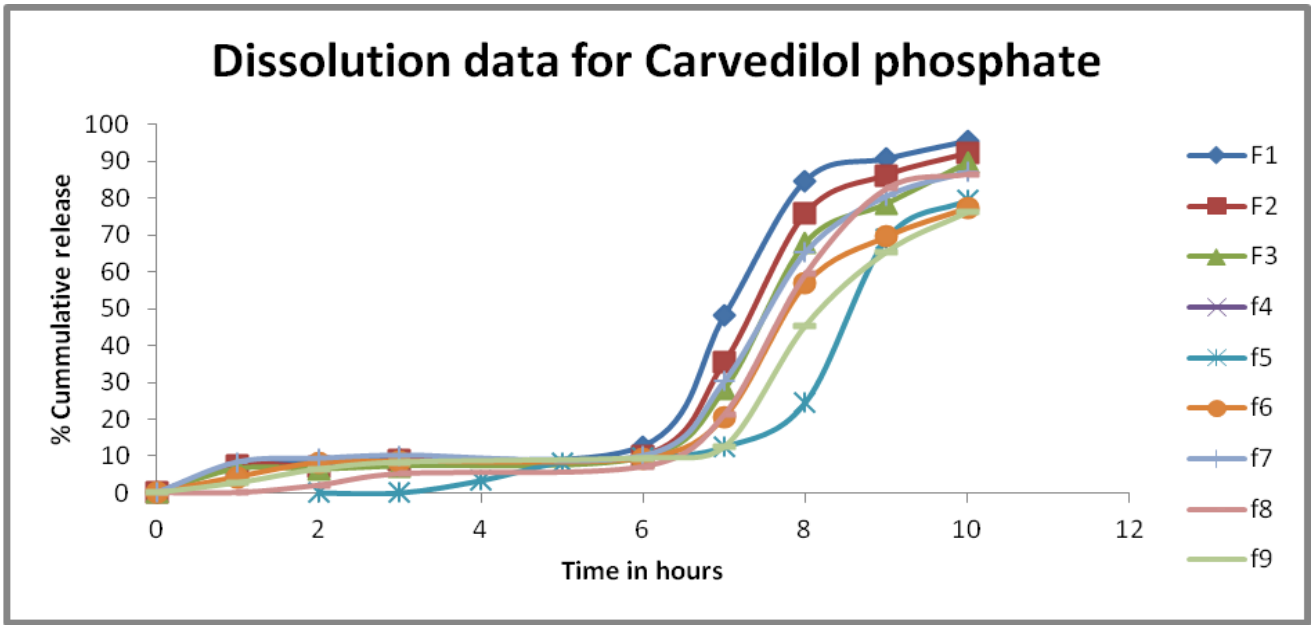

Figure 2: In vitro drug release profile of carvedilol phosphate

Table 3: In vitro release study of prepared tablets

Media	Time Hrs	F1	F2	F3	F4	F5	F6	F7	F8	F9
pH 1.2 HCl buffer	0	0	0	0	0	0	0	0	0	0
	1	7.23	7.44	6.54	5.15	3.34	4.32	8.34	0	2.65
	2	8.21	7.03	6.43	7.13	8.32	8.21	9.32	2.01	6.41
pH 4.5 acetate buffer	3	9.23	8.82	7.23	9.08	9.5	8.44	10.14	5.14	8.24
	6	12.68	10.06	9.56	11.27	12.42	9.39	10.08	7.08	9.38
pH 7.4 phosphate buffer	7	48.1	35.48	28.21	29.63	24.55	20.61	30.37	21.33	12.46
	8	84.73	75.81	67.92	74.49	68.82	56.77	65.41	59.41	45.34
	9	90.61	86.18	78.55	85.32	79.39	69.58	80.64	82.61	65.32
	10	95.39	92.08	89.72	90.7	88.27	77.34	87.24	86.47	76.07

(*n = 3)

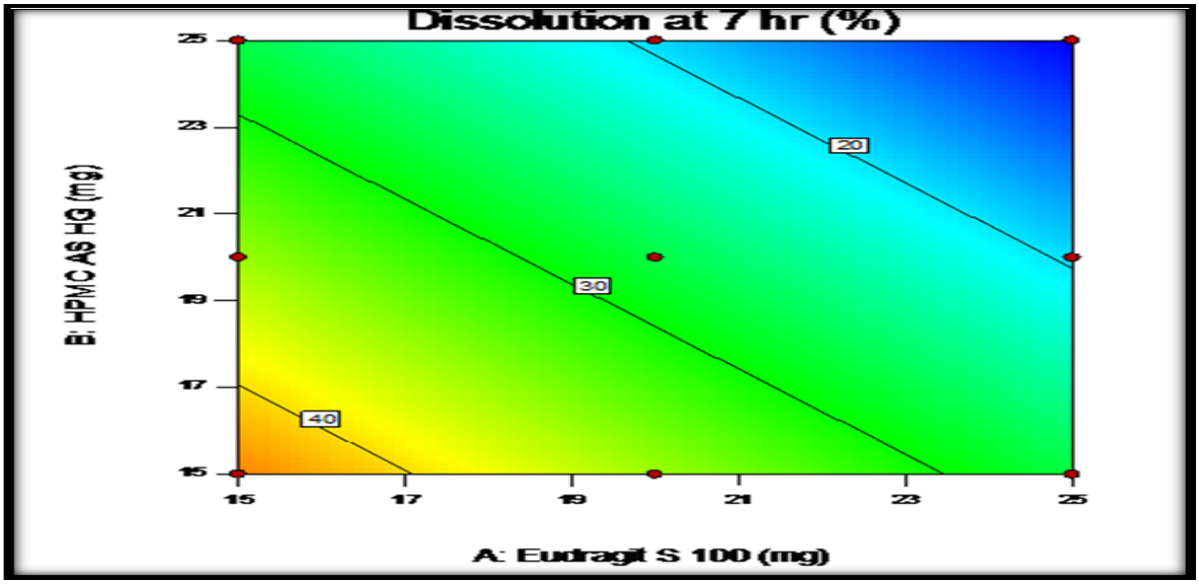

Figure 3: Contour plot for Dissolution at 7 hr (R_1)

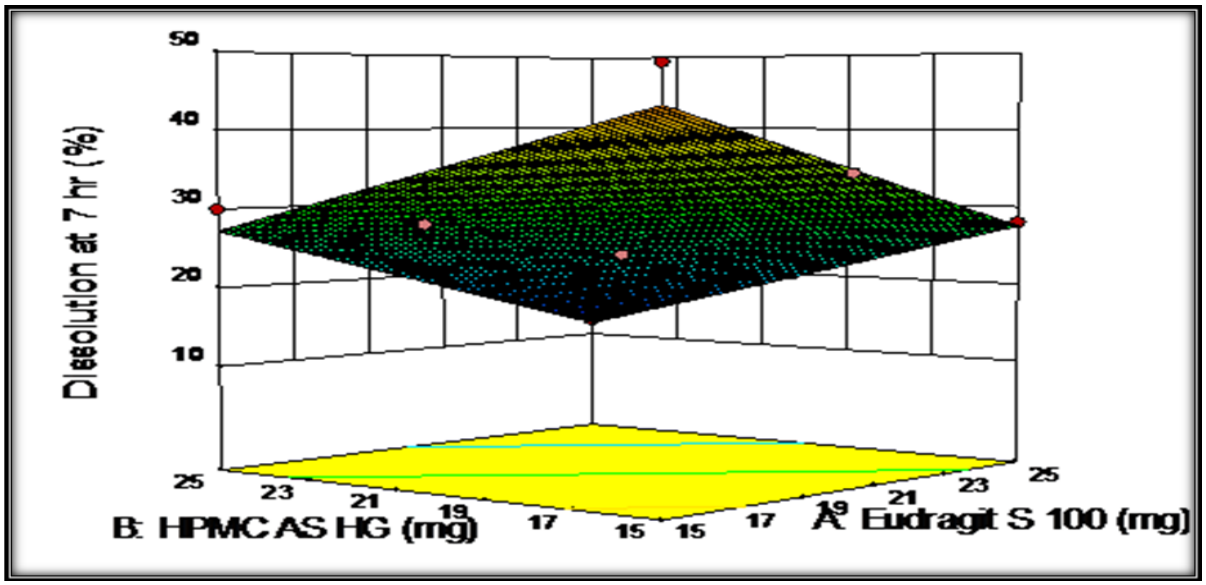

Figure 4: Response surface plot for Dissolution at 7 hr (R_1)

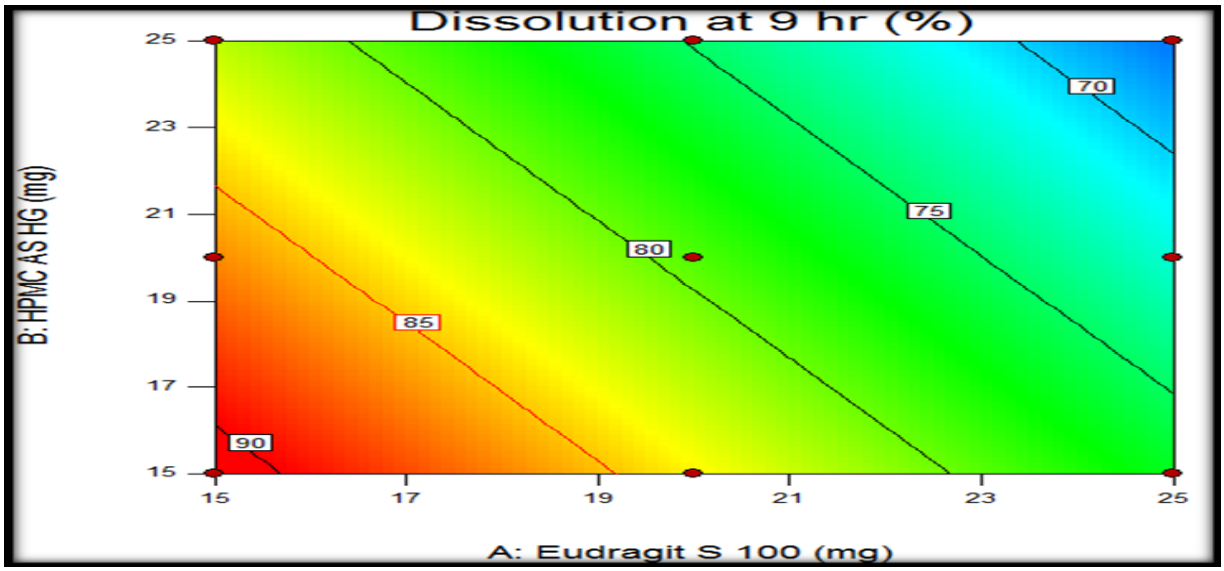

Figure 5: Contour plot for Dissolution at 9 hrs (R_2)

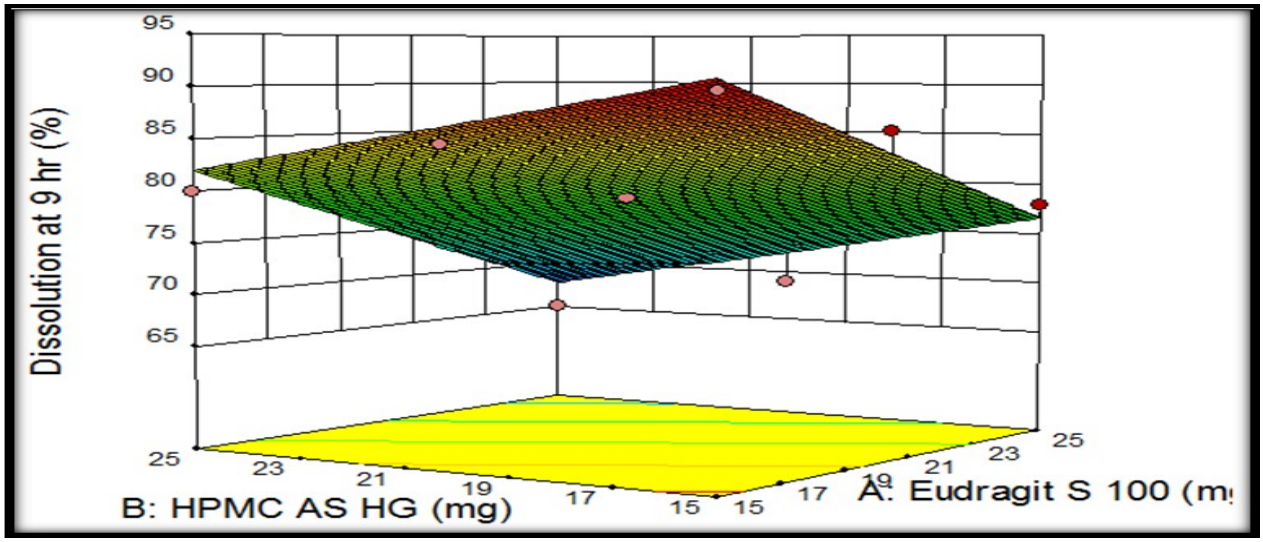

Figure 6: Response surface plot for Dissolution at 9 hrs (R_2)

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