Research Paper
Impact Factor: 3.567
Peer Reviewed Journal

IJMDRR
E- ISSN –2395-1885
ISSN -2395-1877

FORMULATION AND EVALUATION OF FAST DISSOLVING TABLETS OF AN ANTI-ANGINAL DRUG

Mrs. Anasuya Patil* Aniket Jawade **

**Asst. Professor, Department of Pharmaceutical Technology, KLE University's College of Pharmacy, Bengaluru, Karnataka, India.*

M.Pharm, Department of Pharmaceutical Technology, KLE University's College of Pharmacy, Bengaluru, Karnataka, India.

Abstract

The objective of this study was formulation, development and evaluation of Diltiazem hydrochloride fast dissolving tablets. FDTs were prepared by various methods including direct compression method where various superdisintegrants like Crospovidone, Croscarmellose sodium and Sodium starch glycolate in concentration range of 2-6%w/w. Diltiazem hydrochloride FDTs were also prepared by sublimation technique where different subliming agents (5%w/w) camphor, ammonium bicarbonate were used with 6%w/w Sodium starch glycolate as a superdisintegrant. Prepared tablets later exposed to vacuum. The prepared FDTs from two methods were evaluated for weight variation, thickness, drug content, friability, hardness, wetting time, in vitro disintegration time and in-vitro dissolution study. All prepared formulations were showed disintegration time ranging from 25 to 120 sec. All the prepared formulae complied with the pharmacopoeial requirements of the drug contents. F10 prepared formulations gave the less in-vitro disintegration (25.32±0.258sec) and increased percentage cumulative released of 78.11±0.16 after 10min. In conclusion the results of this work suggest that fast dissolving tablets of Diltiazem hydrochloride with rapid disintegration time, fast drug release and good hardness can be efficiently and successfully formulated by employing sublimation methods.

Keywords: Fast Dissolving Tablet, Diltiazem Hydrochloride, Direct Compression Technique And Sublimation Technique.

1. Introduction

FDTs are solid dosage forms rapidly disintegrate in few seconds, when placed on the tongue. Fast dissolving tablets have better patient acceptance and compliance and may offer improved biopharmaceutical properties, efficacy and increased bioavailability compared with conventional oral dosage forms. Patients, particularly paediatric and geriatric patients, have difficulty in swallowing solid dosage forms.[(1)] In order to assist these patients, several fast dissolving drug delivery systems has been developed. Diltiazem is an Antianginal; calcium-channel blocker and is widely used in the management of Prinzmetal's variant angina, chronic stable angina, hypertension, atrial fibrillation or flutter. Diltiazem is well absorbed from the gastrointestinal tract and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. Diltiazem undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. *In-vitro* binding studies show Diltiazem is 70% to 80% bound to plasma proteins. Single oral doses of 30mg to 120 mg of Diltiazem tablets result in detectable plasma levels within 30 to 60 minutes and peak plasma levels 2 to 4 hours after drug administration.[(2)] The aim of the proposed work was to formulate and characterize fast dissolving tablets of Diltiazem Hydrochloride for rapid dissolution of drug and absorption, which may produce rapid onset of action in the management of angina in elderly patients.

2. Materials and Methods

2.1 Materials

Diltiazem hydrochloride was a gift sample from Anglo-French Drugs and Industries Ltd., Bangalore, India, Sodium starch glycolate, camphor, ammonium bicarbonate, mannitol, magnesium stearate, microcrystalline cellulose was supplied from S.D. Fine Chemicals Limited, Mumbai. Aerosil was obtained from Evonik Degussa India Private Ltd. All other ingredients and solvents used were of analytical grade.

2.2 Characterization of drug and excipients.

2.2.a Fourier-transform infra red spectroscopy (FTIR): [(3)]

The IR spectra of the pure drug and drug excipient mixtures were recorded on FTIR spectrophotometer (Shimadzu IR-345, Japan). Samples of 2–3 mg were mixed with about 400 mg of dry potassium bromide then compressed into transparent disks under pressure of 10.000–15.000 psi. The IR spectra were recorded at scanning range from 500–4000 cm^{-1} and resolution of 4 cm^{-1}.

2.2.b Differential Scanning Calorimetry

The samples were hermetically sealed in flat-bottomed aluminum pans and heated over a temperature range of 40-240˚C at a rate of 10˚C/min using alumina as a reference standard. Thermograms of drugs of optimized batches were recorded using a differential scanning calorimeter and were compared.

2.3 Preparation of Diltiazem hydrochloride FDTs.

2.3.1. By Direct Compression Technique:[4,5]

Tablets containing Diltiazem hydrochloride were formulated using various superdisintegrants like Crospovidone(CRP), Croscarmellose sodium(CCS) and Sodium starch glycolate(SSG) in concentrations ranging from 2-6%. The tablets were prepared by direct compression method. The tablets were prepared by direct compression method. All the ingredients were passed through a sieve number 20 prior to mixing. Diltiazem hydrochloride, Mannitol, MCC, aerosil and the superdisintegrants were properly mixed for 30 min in a suitable container to obtain a uniform blend. The blend was further lubricated with magnesium stearate for 5 minutes. The blend was compressed into tablets with an average weight of 200 mg using an 8 mm flat punch in a rotary tablet. Compositions of tablets prepared by direct compression method were shown in table -1.

2.3.2. By Sublimation Technique:[6,7]

Tablets containing Diltiazem hydrochloride were formulated using camphor and ammonium bicarbonate as a subliming agent in concentrations of 5% w/w from the final tablet. The tablets were prepared by direct compression method. All the ingredients were passed through a sieve number 20 prior to mixing. Diltiazem Hydrochloride, Mannitol, MCC, aerosil, Sodium starch glycolate and the camphor were properly mixed for 30 min in a suitable container to obtain a uniform blend. The blend was further lubricated with magnesium stearate for 5 minutes. The blend was compressed into tablets with an average weight of 200 mg using an 8 mm flat punch in a rotary tablet press. Tablets were then placed in an oven at 40˚C till a constant weight is obtained. Compositions of tablets prepared by sublimation technique were shown in table-2.

2.4 Characterization of the prepared Fast dissolving tablets.[8,9]

2.4.1. Weight variation

Ten tablets were individually weighed and average weight was calculated. The individual weight was compared to the average weight. The tablets pass the test if not more than two tablets are outside the percentage limit and if no tablet differs by more than two times the percentage the percentage limit. Ten tablets from each formula were individually weighed and the mean weight was calculated.

2.4.2. Uniformity of FDTs thickness and diameter

The diameter and thickness of 6 tablets were measured using a digital Vernier caliber (China) at three different positions. Results were reported as the mean (±SD) of three measurements.

2.4.3. Friability test

Ten pre-weighed tablets from each formula were tested, accurately placed in the drum of the friabilator (Electrolab EF-2, India) and rotated at 25 rpm for a period of 4 min, then reweighed. The percentage loss in weights was calculated and taken as a measure of friability.

2.4.4. Hardness:

Six tablets were randomly selected and the thickness of each was measured by digital Vernier caliper. Mean and standard deviation were computed and reported.

2.4.5. Drug content uniformity

Ten tablets were randomly selected and allowed to equilibrate with phosphate buffer pH 6.8 which overnight and the solution was filtered after 24 hours. Suitable dilutions were made with the same to get the concentration in Beer's range. Absorbance of the solution was noted at 237nm using phosphate buffer pH 6.8 as a blank and drug content per tablet was calculated.

2.4.6. *In vitro* disintegration time

The test was carried out on 6 tablets using the apparatus (Hanson research, USA). 900 ml phosphate buffer (pH 6.8) at 37± 0.5˚C was used as a disintegration medium and the time taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured in seconds.

2.4.7. *In vitro* dissolution studies

Dissolution study was carried out using USP XXII dissolution test apparatus type II. The dissolution medium used was 900 ml of phosphate buffer pH 6.8 which was maintained at 37°C. The paddle speed was kept at 50 rpm throughout the study.

Five ml of samples was withdrawn at every 2 minutes interval and diluted to 10 ml then 5 ml of fresh dissolution media was replaced maintained at the same temperature was replaced. The samples were analyzed spectrophotometrically at 237nm using phosphate buffer pH 6.8 as blank. The raw dissolution data was analyzed for calculating the amount of drug released and percentage cumulative drug released at different time intervals.

2.4.8. Estimation of wetting time

10ml of phosphate buffer pH 6.8 was added to petri dish containing five circular filter papers of 10 cm diameter. Tablets were carefully placed on the surface of the filter paper and the time required for water to reach upper surface of the tablet was noted as the wetting time. The test results were presented as mean value of three determinations (± SD).

2.4.9. Kinetics Study

For finding out the mechanism of drug release from FDTs, the dissolution data obtained from the experiments were treated with the different release kinetic and mechanism equations.

3. RESULTS AND DISCUSSION

3.1. Characterization of drug and excipients

The infrared spectra of Diltiazem Hydrochloride and other excipients were recorded using a FT-IR spectrophotometer to check for possible drug-excipients interaction. Distinct peak in the region 2960-2850cm^{-1} for C-H aliphatic, C-H aromatic stretching between 3058-3004cm^{-1}, 1650-1000cm^{-1} for C-N amine and C=O stretching between 1650-1900cm^{-1} of the physical mixture was identical to that of pure drug which confirm the compatibility of the drug and excipients.

The DSC thermogram of Diltiazem hydrochloride displayed the characteristics peak at 217˚C compared to its melting point 212˚C. The DSC of formulation F10 showed the thermogram at 157˚C which reveals that drug is complexed with excipients. There was a shift in melting point because of the moisture content and excipients used in the formulation (F10) prepared by sublimation technique.

3.2 Formulation of fast dissolving tablets

The present work was to formulate Fast disintegration tablets of Diltiazem Hydrochloride using various techniques. The preliminary trials were conducted using 2-6% superdisintegrants (CRP, CCS and SSG). Nine batches (F1 to F9) were prepared using various superdisintegrants to formulate the fast dissolving tablets by direct compression method.

In the next approach the tablets were formulated by sublimation technique using 5% camphor and ammonium bicarbonate as a subliming agents. On the basis of result obtained in the preliminary screening studies, the batch containing 6% SSG (F9) prepared from direct compression method showed fastest disintegration. Hence, it was selected for further studies. Sublimation technique is reported to yield porous tablets with low disintegration time and hence this technique was also used in present study.

3.3 Evaluation of Diltiazem hydrochloride FDTs

a. Evaluation of pre-compression properties

The flow properties of the granules (F1-F11) were evaluated by determining the Carr's index, Hausner ratio and angle of repose. Poured density values of different batches were found to range between 0.518 and 0.585 gm/ml^3, whereas tapped density values were found to vary from 0.641 to 0.668gm/ml^3. Carr's index, Hausner ratio and angle of repose were range between 18.24 to 20.30, 1.22 to 1.25, and 21^{o}40' to 29^{o}66' respectively, which indicates that granules prepared exhibit good flow properties.

b. Evaluation of tablet properties

Tablets (F1-F11) were evaluated for tablet properties like thickness, hardness, friability, disintegration time, weight variation, wetting time and drug content uniformity etc. Tablet thickness was found to range from 2.88±0.03 to 3.18±0.03 mm. Tablets of all the batches were found out to exhibit sufficient hardness, which ranged from 3.10±0.23 to 4.00±0.13 Kg/cm^2. Wetting time of the tablet was found to be in the range of 27.74±1.001sec to 32.46±2.488 sec. Friability, weight variation test and percentage drug content uniformity met the specification given in the literature.

Disintegration time of formulations (F1 to F9) prepared by direct compression method was found to be in the range 28.67±0.160sec to 135.40±0.469sec. Increase in the concentration of superdisintegrants from 2% to 6%, decreases the disintegration time of the tablets. Among the three superdisintegrants used, rapid disintegration was seen in formulation

containing SSG. Increase in the concentration of was found to be beneficial in reducing the disintegration time. *In vitro* dissolution study of formulation (F9) containing 6% SSG, (which gave lowest disintegration time of 28.67±0.160sec) showed an increased cumulative release of 76.005±0.134 after 10 min. This method was found to give a low disintegration time and increased cumulative release after 10 min.

Disintegration time of formulations (F10 and F11) prepared by sublimation technique was found to be in the range 25.32±0.258sec to 26.12±0.215sec. *In vitro* dissolution study of formulation of F10 (which gave least disintegration time of 25.32±0.258sec) showed a cumulative release of 78.115 ± 0.162 after 10 min. Lesser disintegration time of 25.32±0.258sec was obtained with 5% camphor as a subliming agent using 6% SSG in tablets prepared by sublimation technique. Thus sublimation technique was thus found to give a low disintegration time and a good release after 10 min.

The various techniques used for fast dissolving tablets of Diltiazem Hydrochloride were compared. It was found that formulation F10 prepared by sublimation technique were beneficial in obtaining the low disintegration time 25.32sec (F10) and increased cumulative release after 10min as compared to formulation(F9) containing 6% SSG prepared by direct compression method shown in (Fig.-3). The porous structure is responsible for faster water uptake, so it facilitates the action of SSG in bringing about faster disintegration. However this technique would definitely be beneficial for drugs with a higher dose where low disintegration time can be achieved using super disintegrant alone.

Formulation F10 (prepared by sublimation technique) was compared with pure drug. It was found that the formulated fast disintegration tablets showed an increase in % CR of 78.115 ± 0.162 after 10min compared to the pure drug which was found to be 40.86±1 respectively.

To know the order of release the release rates were subjected to kinetic studies. The diffusion data of the optimized formulation fitted well into Peppas release kinetics showed in Fig-4 which indicates that release is controlled by swelling which could be due to the presence of SSG.

4. Conclusion

From the present work, it can be concluded that among the various techniques used, sublimation technique is best suitable in the preparation of Fast disintegration tablets of low dose drug like Diltiazem hydrochloride. Use of 5%w/w camphor as a subliming agent was further found to be beneficial in obtaining a product with reduced disintegration time and increased % cumulative release.

Thus it can be concluded that FDTs with less disintegration time can be prepared by sublimation technique using SSG in concentration of 6%. The prepared FDTs disintegrate within few seconds without need of water; thereby enhance the absorption leading to increased bioavailability of Diltiazem hydrochloride.

References

1. Amarjit S, Rajesh J. United states Patent No.7122198. Fast dissolving composition with prolonged sweet taste.
2. Martindale. The complete drug reference. In: Sweetman SC, editor. 34th ed. London: Pharmaceutical Press; 2002.
3. Kemp W. Organic spectroscopy, 3rd ed. London: Palgrave 1991: p. 19-96.
4. Indurwade NH, Rajyaguru TH, Nakhat PD. Novel approach– Fast dissolving tablets. Indian Drugs 2002;39(8):405-414.
5. Sreenivas SA, Dandagi PM, Gadad AP, Godbole AM, Hiremath SP, Mastiholimath VS, *et al.* Orodispersible tablets: new-fangled drug delivery system-a review. Ind. J. pharm. Educ. Res. 2005;39(4):177-181.
6. Biradar SS, Bhagavati ST, Kuppasad IJ. Fast dissolving drug delivery systems: A brief overview. Int. J. Pharmacol. 2006;4(2):1-7.
7. Dinesh kumar V, Ira Sharma and Vipin Sharma. A comprehensive review on fast dissolving tablet technology. J. App. Pharm. Sci. 01 (05); 2011:50-58.
8. Lachman L, Liberman HA, Kanig JL. The theory and practice of industrial pharmacy. 3rded. Bombay: Varghese publishing house; 1991. p. 296-303.
9. Skoog DA, Holler FJ, Nieman TA. Principles of instrumental analysis. 5th ed. Singapore: Thomson Asia Pvt Ltd 1998: p. 380-426.

Table 1: Composition of Fast Dissolving Tablets of Diltiazem Hydrochloride.

Ingredients	Formula code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Diltiazem Hydrochloride	60	60	60	60	60	60	60	60	60
Crospovidone	4	8	12	--	--	--	--	--	--
Crospovidone	--	--	--	4	8	12	--	--	--
Sodium starch glycolate	--	--	--	--	--	--	4	8	12
Microcrystalline cellulose	74	70	66	74	70	66	74	70	66
Mannitol	58	58	58	58	58	58	58	58	58
Magnesium stearate	2	2	2	2	2	2	2	2	2
Aerosil	2	2	2	2	2	2	2	2	2

Table 2: Composition of Fast Dissolving Tablets of Diltiazem Hydrochloride.

Ingredients	Formula code	
	F10	F11
Diltiazem Hydrochloride	60	60
Camphor	10	--
Ammonium bicarbonate	--	10
Sodium starch glycolate	12	12
Microcrystalline cellulose	56	56
Mannitol	58	58
Magnesium stearate	2	2
Aerosil	2	2

Table 3. Evaluation of FDTs of Diltiazem hydrochloride prepared by direct compression method.

*Average of 3 readings ± SD

Formula	Mean* thickness (cm)±S.D	% Drug* content±S.D	% Friability	Hardness* (kg)±S.D	Disintegration* time(sec)± S.D	Wetting time±S.D*(sec)
F1	3.13±0.01	84.50±0.008	0.44	3.17±0.30	120.40±0.469	68.88±2.045
F2	3.18±0.03	84.38±0.015	0.63	3.12±0.34	85.27±0.782	66.55±1.002
F3	3.17±0.01	84.60±0.007	0.75	3.53±0.25	50.40±0.369	60.79±1.712
F4	2.98±0.01	85.00±0.041	0.32	3.14±0.20	110.52±0.469	70.69±0.560
F5	3.13±0.01	84.80±0.006	0.42	3.23±0.15	75.85±0.813	68.17±0.850
F6	3.15±0.03	84.93±0.020	0.54	3.36±0.12	40.91±0.671	65.66±0.995
F7	2.88±0.03	84.63±0.014	0.73	3.23±0.27	70.66±0.125	62.42±1.100
F8	3.02±0.07	85.05±0.005	0.66	3.26±0.19	40.96±0.0145	58.28±1.564
F9	2.97±0.02	85.20±0.011	0.51	3.45±0.22	28.67±0.160	55.87±1.014

Table 4. Evaluation of FDTs of Diltiazem hydrochloride prepared by sublimation method.

Formula	Mean thickness* (cm)±S.D	% Drug content±S.D	% Friability	Hardness* (kg)±S.D	Disintegration time*(sec)±S.D	Wetting time*(sec)±S.D
F10	3.16±0.02	86.00±0.008	0.83	3.13±0.29	25.32±0.258	40.74±1.001
F11	3.18±0.01	84.59±0.009	0.48	3.10±0.23	26.12±0.215	50.88±2.045

*Average of 3 readings ± SD

IJMDRR
E- ISSN –2395-1885
ISSN -2395-1877

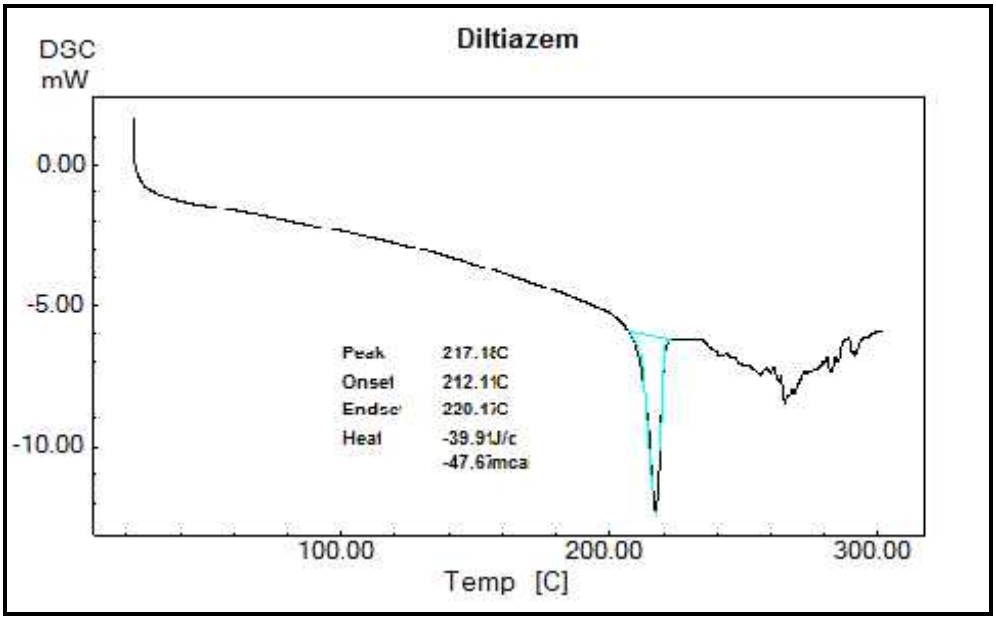

Fig.1. DSC of Diltiazem Hydrochloride.

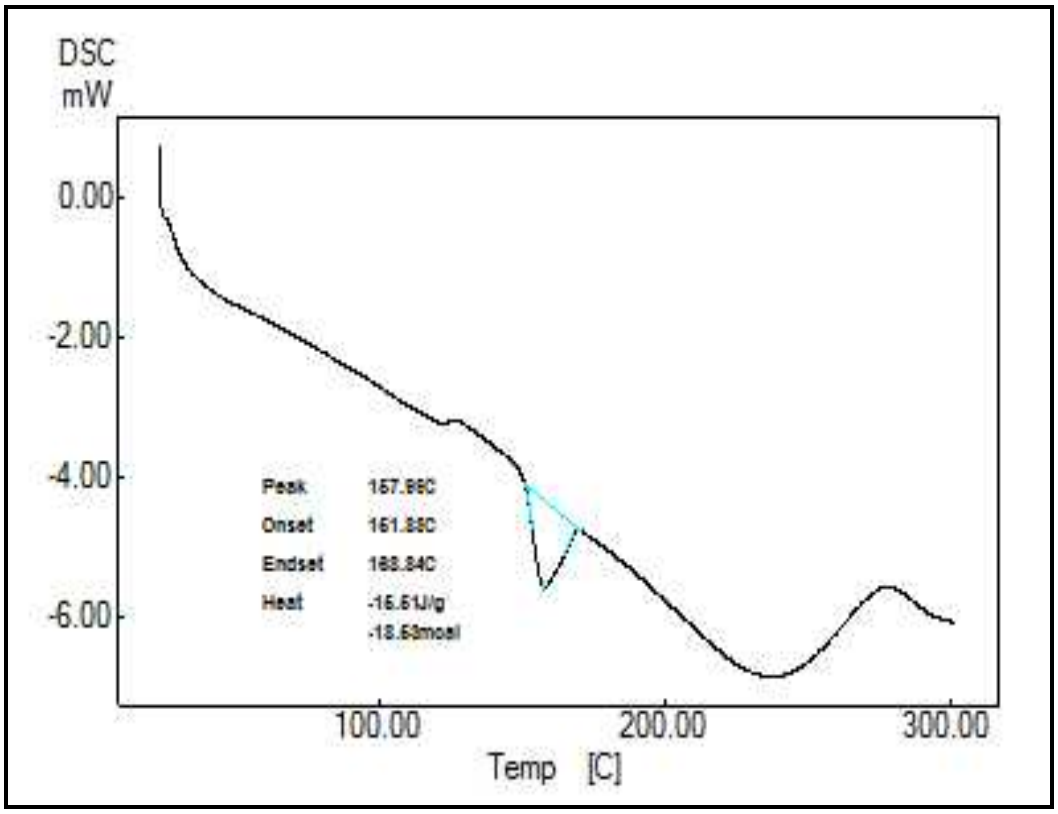

Fig.2. DSC of optimized formulation F10.

IJMDRR
E- ISSN –2395-1885
ISSN -2395-1877

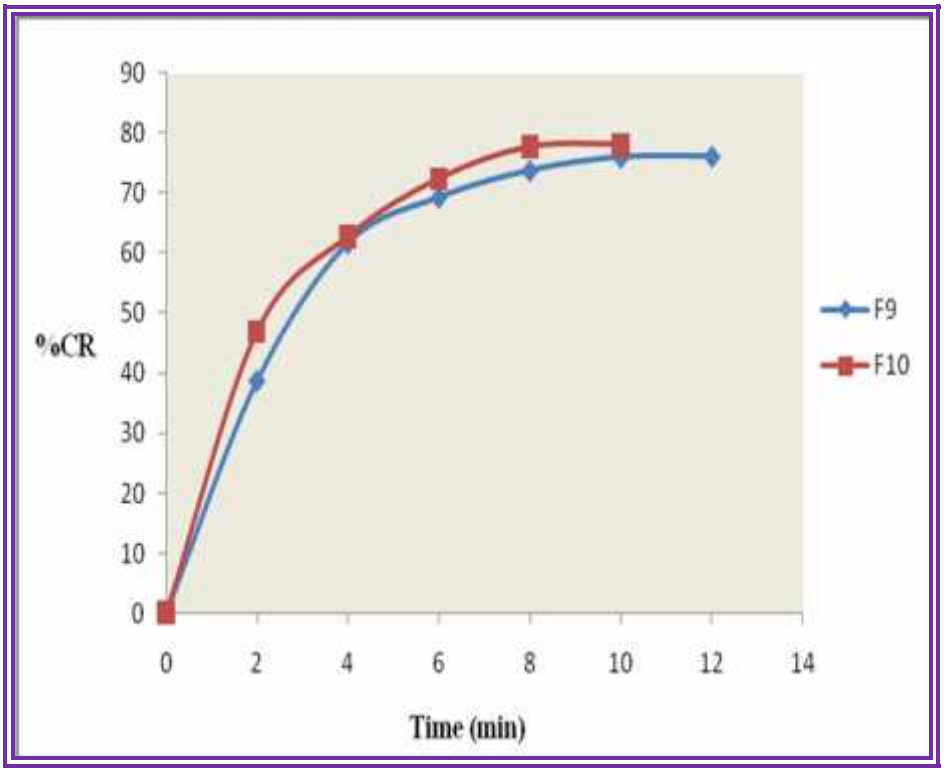

Fig.3. *In-vitro* dissolution profile of F9 and F10.

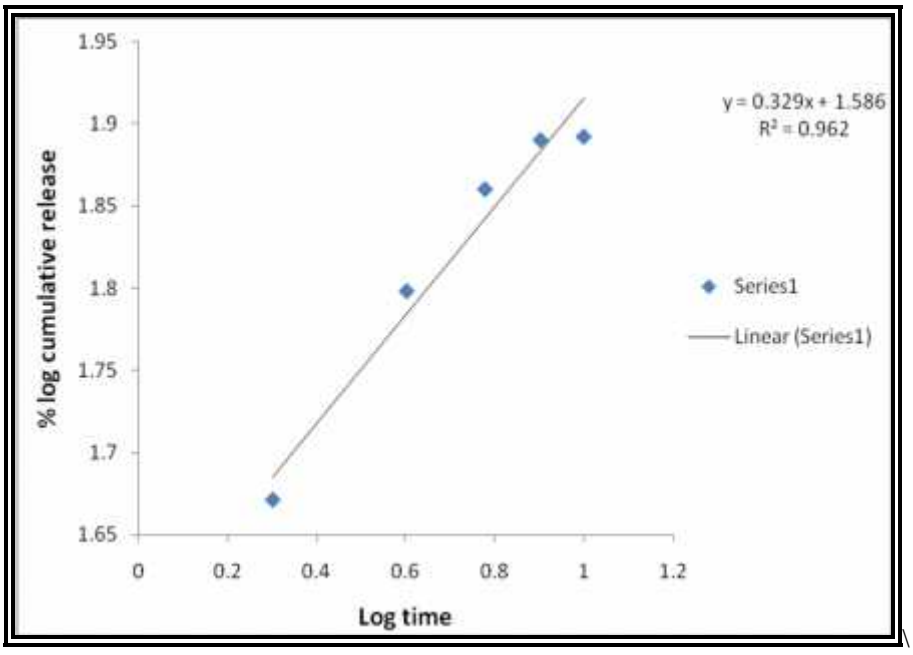

Fig.4 Korsemeyer-Peppas Plot of optimized formulation.