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Development and Optimization of Immediate Release Pellets for Combined Dose Therapy.

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ABSTRACT

The study was undertaken with an aim to improve the efficacy and reduce the adverse effect of drug, by combination therapy of Diltiazem HCL and Quercetin dihydrate. In the present research 22 formulations were developed using design expert software with response surface methodology. In which the effect of superdisintegrant, type of superdisintegrant, effect of diluents, formation of solid dispersion studied for their *in vitro* release from pellets. The result depicted that the formulation containing superdisintegrant crospovidone, diluent lactose and presence of surfactant showed good disintegration time and in vitro drug release.

Key words: Diltiazem HCL, Quercetin, Pellets, Immediate release

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INTRODUCTION

Pellets are agglomerates of fine powders or granules of bulk drugs and excipients. They consist of small, free flowing, spherical or semi-spherical solid units, typically from about 0.5mm to 1.5mm, and are intended usually for oral administration. Pellets are rapidly and homogeneously distributed into the gastrointestinal tract in spite of feeding or fasting condition thus reduce the risk of high local concentration and side effects increase the contract region between drug and the GIT. [1].Diltiazem HCL one member of calcium channel blockers widely used in the treatment of angina pectoris and Hypertension[2]. DTZ is extensively metabolized by the liver and excreted by the kidney and it is absorbed fraction up to about 80%. However, due to an extensive first effect, Diltiazem HCL is subject to an absolute bioavailability of about 40%. Frequent administration of immediate release preparations is often recommended to maintain effective blood plasma levels of Diltiazem HCL. It also can reduce early reinteraction rates in patients with non Q-wave MI left ventricular functions. Sinus bradycardia and AV block occurs frequently often in association with comcommitant β-blockers. CHF can worsen in patients with underlying left ventricular dysfunction. Quercetin is member of the class of flavonoids termed as flavonols. They are widely distributed in the plant kingdom[3]. Quercetin is found abundantly in redwine, green tea, onions, berries, citrus fruits, parsley, apples, and garlic. Mitochondria play a critical role in myocardial recovery from ischemia-reperfusion (I-R) damage. Quercetin treatment significantally decreases the impairment of cardiac function following I-R. This protective effect improves mitochondrial function after I-R. Which indicate the Quercetin is cardio protective. Quercetin improve the contractile function of the left ventricular myocardium decreases the incidence of heart rate and conductivity disorders, limit the ischemic damage area, promote the preservation of the vessels integrity, improve the coronary circulation and the prevent intravascular thrombus formation. Quercetin may also modulate ion channels, and possess structural similarities to several antiarrhythmic voltage-gated sodium channels inhibitors. By inhibiting cardiac voltage gated sodium channels. Hence the attempt is made to combine Diltiazem HCl and Quercetin dihyrate in form of immediate release pellets.

In the present study different variables were studied like type of superdisintegrant, concentration of superdisintegrant, presence of surfactant, type of diluents on % drug release.

MATERIALS AND METHOD

Diltiazem HCl was a gift sample from Ajanta Pharma Mumbai, Quercetin Dihydrate and Poloxamer 407 were purchased from Otto chemie Mumbai, Di.calcium phosphate was a gift

dependent and independent variables(Table 1). Here Lactose was used as a soluble diluent and Di.calcium phosphate was used as an insoluble diluent .(Table no 2)

Table 1 Formulation Variable Details

Independent Variables	**Level**	
	-1	+1
Effect of Solid dispersion formation (X1)	In solid Dispersion form	Plain drug
Type of Superdisintegrant(X2)	Crospovidone	Sodium Starch Glycolate
Conc. of Superdisintegrant (X3)	5	7.5
Type of Diluents(X4)	Insoluble	Soluble
Dependant Variables	Y1	Disintegration Time
	Y2	% Drug Release For Diltiazem HCl
	Y3	%Drug Release For Quercetin

Table 2 Formulation table as per factorial design

Formulation	**Effect of Conc. of Superdisintegrant(%)**	**Effect of type of Superdisintegrant**	**Effect of Solid Dispersion formation**	**Effect of type of Diluent**
F1	7.5	Crospovidone	In solid Dispersion form	Insoluble
F2	7.5	SSG	In solid Dispersion form	Soluble
F3	6.25	Crospovidone	Plain drug	Soluble
F4	5	SSG	In solid Dispersion form	Soluble
F5	6.25	SSG	In solid Dispersion form	Soluble
F6	5	SSG	In solid Dispersion form	Insoluble
F7	6.25	SSG	Plain drug	Insoluble
F8	7.5	SSG	Plain drug	Soluble
F9	6.25	Crospovidone	In solid Dispersion form	Insoluble
F10	6.25	SSG	In solid Dispersion form	Soluble
F11	5	Crospovidone	In solid Dispersion form	Soluble
F12	7.5	Crospovidone	Plain drug	Insoluble
F13	6.25	SSG	Plain drug	Insoluble
F14	5	Crospovidone	Plain drug	Insoluble
F15	7.5	Crospovidone	Plain drug	Soluble
F16	7.5	Crospovidone	In solid Dispersion form	Soluble
F17	7.5	SSG	In solid Dispersion form	Insoluble
F18	5	SSG	Plain drug	Soluble
F19	5	Crospovidone	Plain drug	Insoluble
F20	6.25	Crospovidone	Plain drug	Soluble
F21	7.5	SSG	Without	Insoluble
F22	6.25	Crospovidone	With	Insoluble

Drug :

30 mg of the Diltiazem HCl and 125 mg of the Quercetin dihydrate kept constant for all formulations. 62.5 mg of the Poloxamer 407 used for with surfactant formulation.

Evaluation of Pellets:

Important properties such as Carr's index, Hausner's ratio, angle of repose of pellets, and disintegration test were determined using the standard procedure. Particle Size analysis was done using sieve analysis technique.

In vitro Dissolution:

The dissolution of the pellets was performed using USP XXII apparatus type II (paddle method) using 900 ml of the 0.1N HCL acid as the dissolution media thatwas maintained at $37^0C \pm 2^0C$ and stirred at 50 RPM. Aliquot's of 1ml sample was withdrawn with a bulb pipette with equal volume of 0.1N HCL and the aliquots were filtered using Whatman filter paper no.1. Filtrate was analyzed spectrophotometrically at 237 nm and 372 nm for Diltiazem HCl and Quercetin dihydrate respectively, and the percentage drug release at different time intervals was calculated.

RESULT AND DISCUSSION

Quercetin Being an Insoluble drug solid dispersion of it were prepared using various concentration ratios in which 1: 0.5 ratio of drug as to surfactant polymer gave very good solubility and was used in the pellet formulation.

IR spectra of the Drugs and Formulation were recorded in the 4000–400 cm^{-1}.(Fig 1) The prominent peak of Diltiazem HCl and Quercetin dihydrate showed that there was no incompatibility between drug and excipient used in the formulation. The DSC thermogram of the formulation showed two sharp peaks of. The Diltiazem HCl at 206.62ºC while Quercetin dihydrate at 300ºC there was no change in the peak of the drug into the formulation.(Figure 2-4)

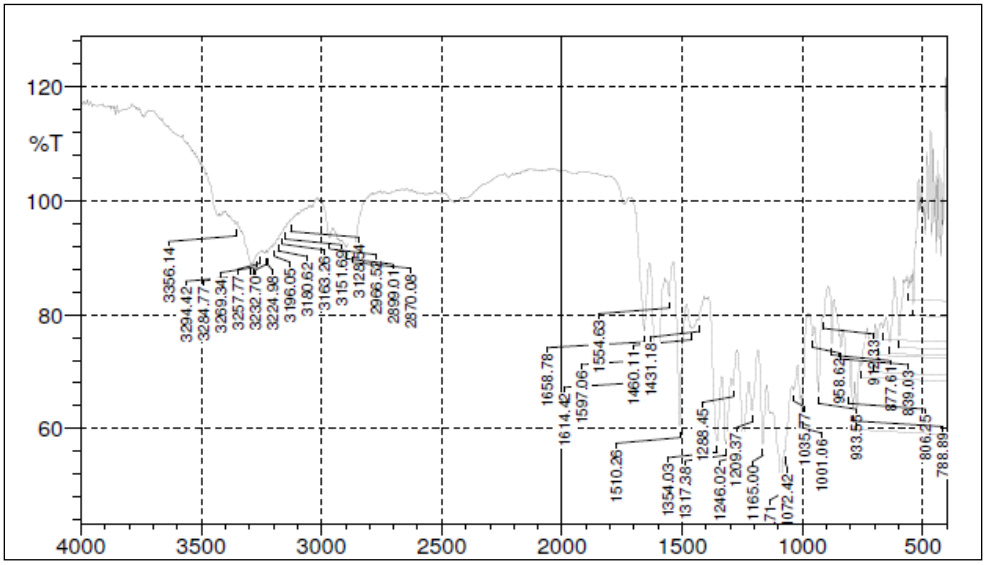

Figure 1 FTIR Spectrum of the Drugs with excipients

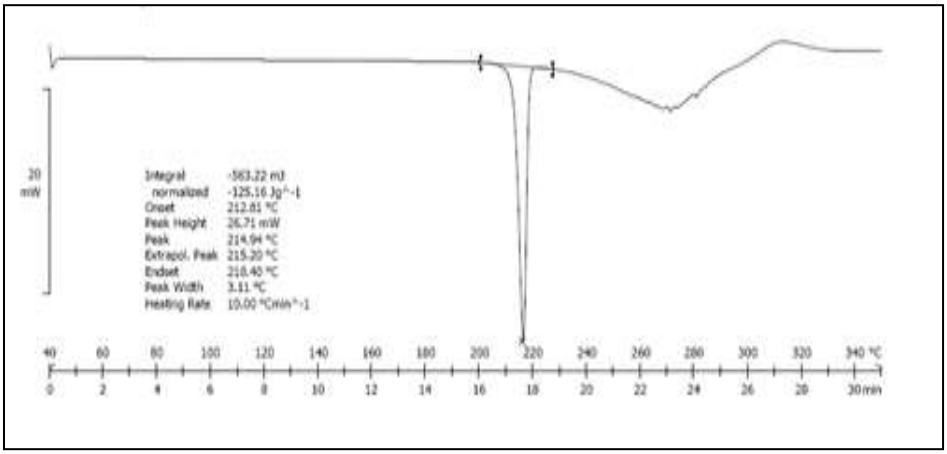

Figure 2 DSC Spectrum of the Diltiazem HCl

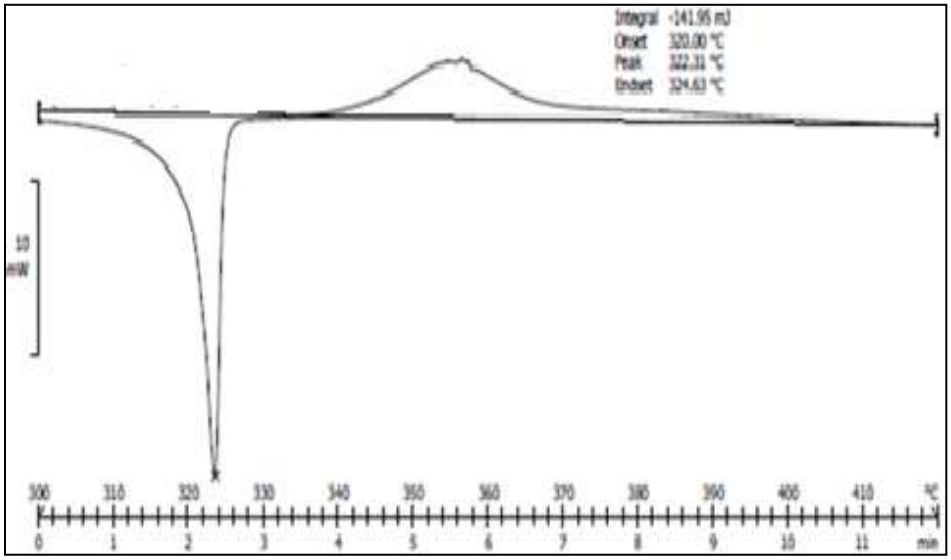

Figure 3 DSC spectrum of the Quercetin

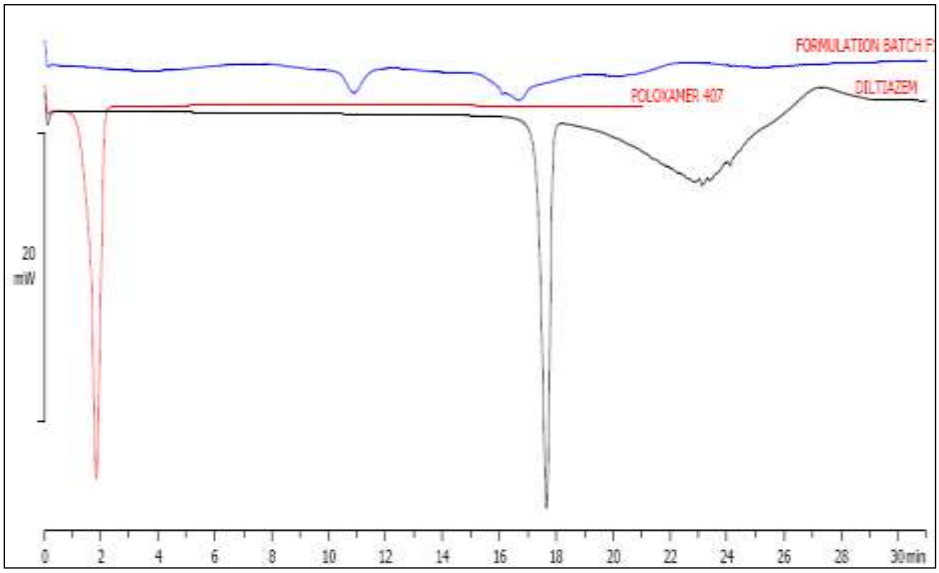

Figure 4 Overlay spectrum of the drug and polymer

Evaluation of pellets formulation :

Table 3 Evaluation of pellets

Parameter / Formulation	Bulk density(gm/ml)	Tapped density(gm/ml)	Angle of repose(degree)	Carr's index(%)	Hausner's ratio
F1	0.15±0.01	0.62±0.01	31.79±0.57	16±0.01	1.21±0.03
F2	0.15±0.01	0.46±0.01	24.22±0.45	17±0.02	1.21±0.01
F3	0.14±0.01	0.44±0.01	38.65±0.35	16±0.02	1.17±0.03
F4	0.15±0.02	0.62±0.03	28.36±0.54	16±0.03	1.12±0.02
F5	0.15±0.02	0.57±0.01	26.10±0.65	17±0.01	1.20±0.03
F6	0.14±0.01	0.60±0.02	29.68±0.24	15±0.01	1.15±0.01
F7	0.16±0.02	0.50±0.02	32.61±0.29	15±0.02	1.13±0.03
F8	0.15±0.03	0.37±0.01	32.70±0.30	16±0.03	1.18±0.02
F9	0.15±0.03	0.65±0.03	27.9±0.57	15±0.02	1.19±0.02
F10	0.15±0.02	0.57±0.01	26.10±0.65	17±0.01	1.20±0.03
F11	0.15±0.01	0.62±0.01	30.54±0.46	17±0.02	1.20±0.03
F12	0.15±0.01	0.53±0.03	30.96±.36	16±0.02	1.20±0.01
F13	0.16±0.02	0.50±0.02	32.61±0.29	15±0.02	1.13±0.03
F14	0.14±0.01	0.53±0.01	27.47±0.37	17±0.01	1.15±0.01
F15	0.16±0.01	0.33±0.02	25.64±0.54	16±0.02	1.13±0.01
F16	***0.15±0.01***	***0.57±0.01***	***26.56±0.24***	***16±0.01***	***1.18±0.02***
F17	0.15±0.01	0.60±0.01	33.42±0.56	17±0.03	1.19±0.03
F18	0.15±0.01	0.37±0.02	25.64±0.54	15±0.01	1.20±0.02
F19	0.14±0.01	0.50±0.02	27.47±0.37	17±0.01	1.15±0.01
F20	0.14±0.01	0.44±0.01	38.65±0.35	16±0.02	1.17±0.03
F21	0.15±0.01	0.53±0.01	32.21±0.35	15±0.01	1.21±0.03
F22	0.15±0.03	0.65±0.03	27.9±0.57	15±0.02	1.19±0.02

The formulations were evaluated for its micromeritic properties and found that all the batches were in the range(Table 3).

Particle size analysis

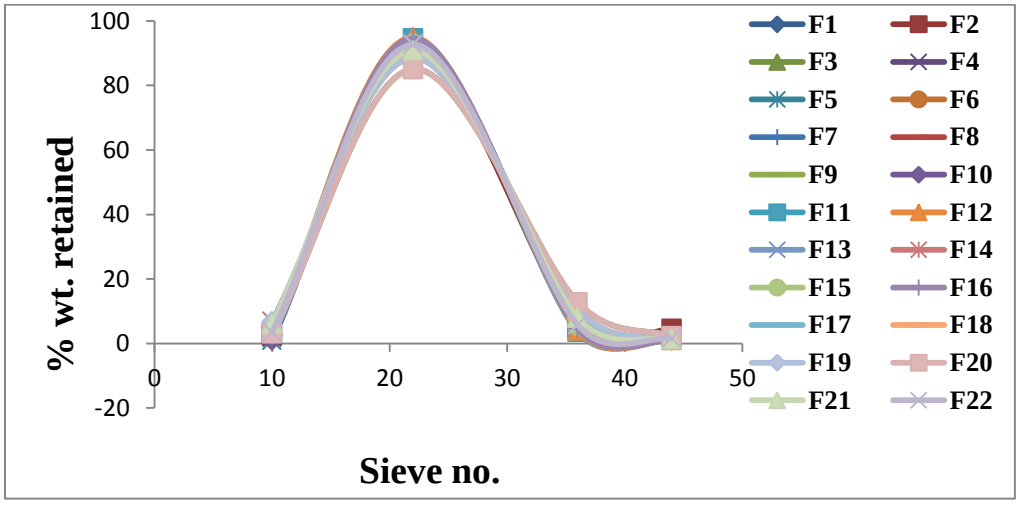

Figure 5 Particle Size Analysis of pellets

It is found that the particle size of the pellets was retained on mesh size #22.

% weight retained on sieve = wt. retained on sieve/ total weight taken X 100

Particle size analysis of the pellets calculated by using below formula. Particle size analysis indicates that nearly 90% ≥ of particles were retained on sieve size 710µm.

Disintegration studies:

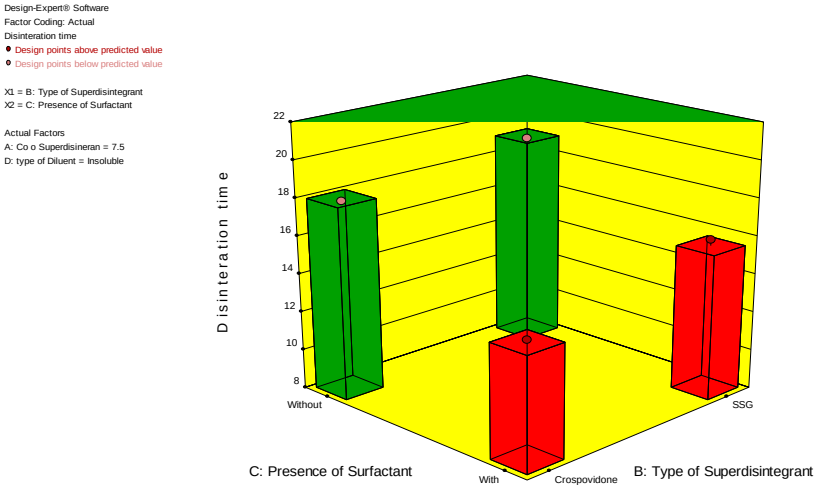

Figure 6 Response surface Plot for Disintegration of pellets

When the concentration of superdisintegrant was increased the disintegration time was decreased. The concentration of superdisintegrant from 5 % to 7.5% helps to decrease the disintegration time. 7.5 % concentration of crospovidone showed less disintegration time than sodium starch glycolate. Concentration of superdisintegrant affect on disintegration time of both the drugs. Concentration of crospovidone has positive effect due to its capillary action and hydration. While sodium starch glycolate affect because of its mechanism of formation of viscous gel layer [4,5].

The use of superdisintegrant for preparation of immediate release pellets is highly effective and feasible. The superdisintegrant crospovidone were used to achieve a fast disintegration of the pellets. These superdisintegrant accelerate disintegration of pellets by virtue of their ability to absorb a large amount of water when exposed to an aqueous environment. The absorption of water results in the breaking of the particle and therefore a faster disintegration this disintegration is reported to have an effect on dissolution characteristic as well [4,5]

Increase in the concentration of SSG from 5% to 7.5 % resulted in a significant increase in the disintegration time of the pellets. This dissimilar behavior of crospovidone and SSG on the disintegration time can be attributed to the difference in their mechanism of disintegration. The concentration of the superdisintegrant crospovidone had a positive effect on the disintegration of the pellet increasing the concentration of the crospovidone resulted in faster disintegration of the

pellets, which may be due to a rapid capillary activity and pronounced hydration with little tendency for gel formation. On the contrary when the concentration of SSG was increased it had a negative effect on the disintegration of the pellets. This negative effect may be due to the formation of viscous gel layer by SSG which may impede further penetration of the disintegration medium and hinder the disintegration of the pellets content

The surfactant polymers were mainly added to form solid dispersions of poorly soluble Quercetin. It was found that he disintegration time of the formulation was decreased when there was presence of surfactant. Presence of surfactant prevents aggregation of the fine particles and providing larger surface area. Polymer helps to decrease the interfacial tension between the medium and the drug [6-8] Lactose and Di.calcium phosphate which are soluble and insoluble diluent respectively does not affect directly on the disintegration time of the pellets but modifying them[9]. In presence of the soluble diluent disintegration time was less than insoluble diluent.

***In vitro* dissolution studies**

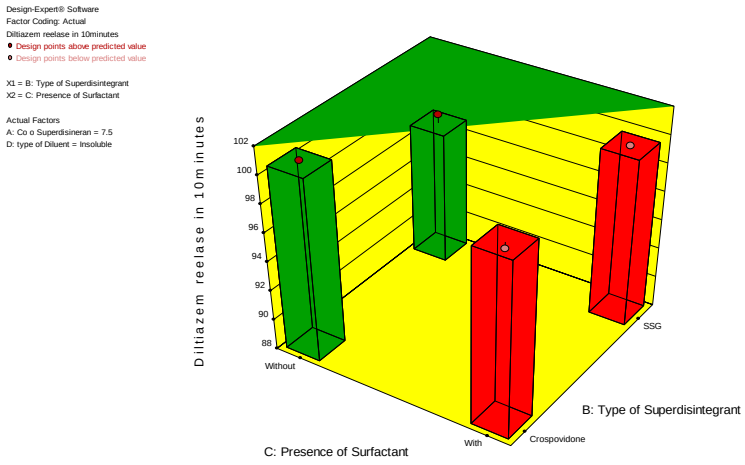

Figure 7 Effect of Insoluble diluents on release of Diltiazem Hydrochloride

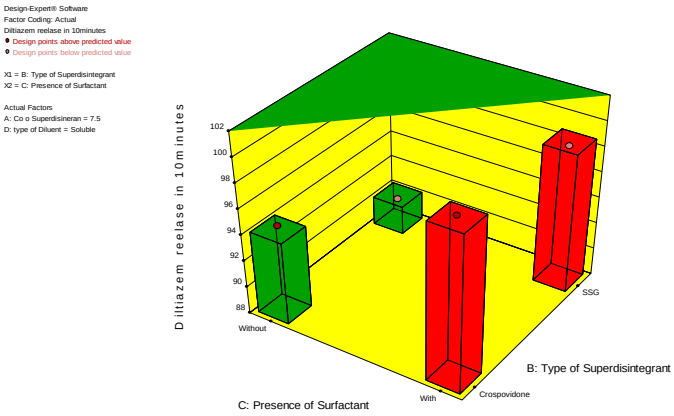

Figure 8 Effect of soluble diluents on release of Diltiazem Hydrochloride

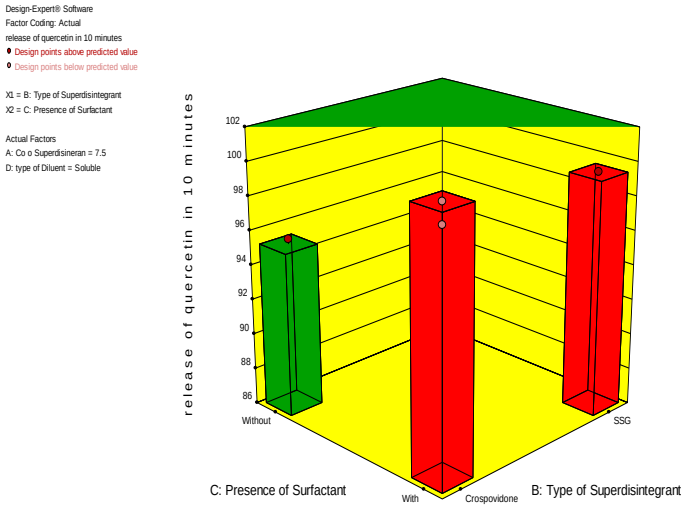

Figure 9 Quercetin Release with higher conc of Superdisintegrant and soluble diluent

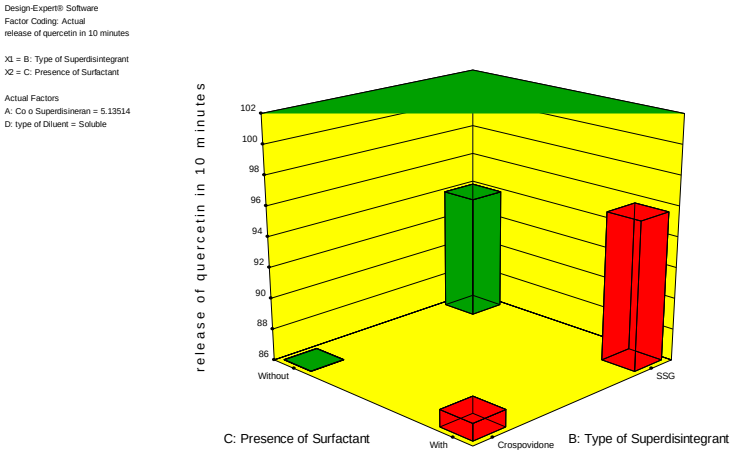

Figure 10 Quercetin Release with lower conc of Superdisintegrant and soluble diluent

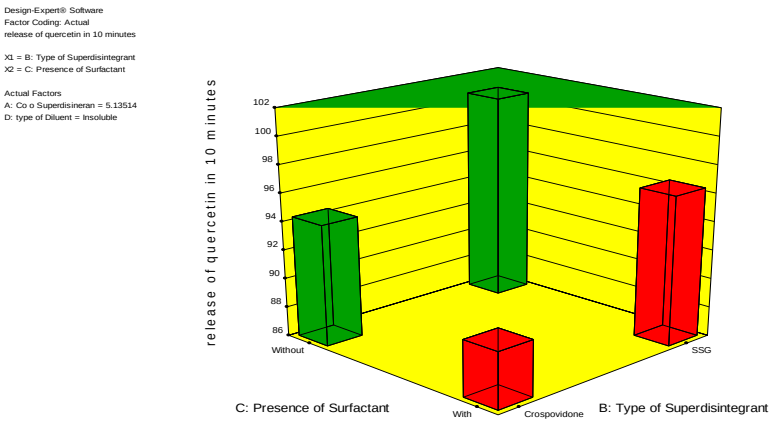

Figure 11 Quercetin Release with lower conc of Superdisintegrant and insoluble diluent

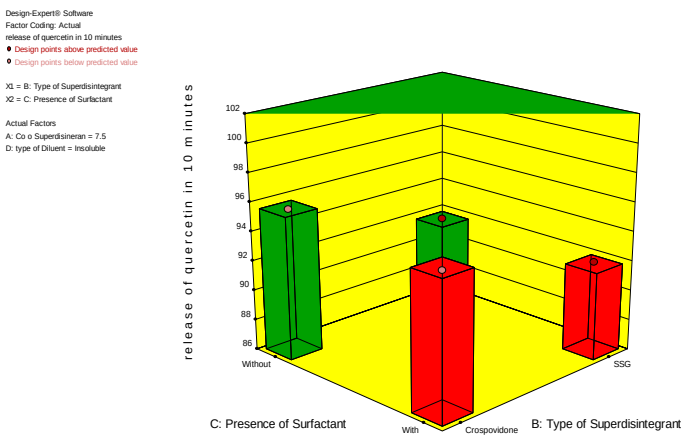

Figure 12 Quercetin Release with higher conc of Superdisintegrant and insoluble diluent

Drug release was increased with increase in the concentration of superdisintegrant from 5% to 7.5%. Drug release of both the drug was 96 % with crospovidone. In case of Diltiazem HCl when the Concentration of Crospovidone was increased the disintegration time was decreased. And when the concentration of Crospovidone was 5% the drug release was more than 7.5% concentration. But in case of Quercetin dihydrate when the concentration of Crospovidone increased the drug release was increased (Figure 9,10,11,12).

Concentration of superdisintegrant directly does not affect on the drug release. The drug release was more with superdisintegrant like crospovidone than sodium starch glycolate. When the concentration of the crospovidone was 7.5% the drug release was more than the same concentration of sodium starch glycolate. Both of the superdisintegrant having different mechanism on drug release.

The concentration of the superdisintegrant Crospovidone had a positive effect which may be due to a rapid capillary activity and pronounced hydration with little tendency for gel formation. On the contrary SSG had a negative effect on the drug release of the pellets. This negative effect may be due to the formation of viscous gel layer by SSG which may impede further penetration of the dissolution medium

With the formation of solid dispersion in the formulation both the drug showed 96% drug release. Diltiazem HCl was water soluble drug and Quercetin was not a water soluble drug hence presence of surfactant affects on the drug release of the Quercetin. Poloxamer 407 helps to increase the drug release of Quercetin(Figure 11,12). Because Quercetin showed minimum drug release when there was absence of solid dispersion. Poloxamer 407 helps to increase the surface area and surface free energy resulting in the enhancement of the dissolution rate. The faster dissolution rate merely

based on the particle size without anything to do with energy changes. The presence of carrier (Poloxamer 407) may also prevent aggregation of fine drug particles, thereby providing a larger surface area for dissolution[10,11].

The wetting property was also increased due to the surfactant property of the polymer, resulting in decreased interfacial tension between the medium and the drug; and thus enhance the dissolution rate of the drug. The presence of polymer was also expected to inhibit the crystal growth of the drug which may facilitate faster dissolution.

When the soluble diluent was present in the formulation the drug release of both the drug was 94% and when the insoluble diluent was present drug release was up to 100% for Diltiazem HCl and 94% for Quercetin (Figure 7,8, 9 ,10, 11) .

Lactose which is a soluble diluent does not affect on the drug release but modifying the drug release[12]. Di. Calcium phosphate does not affect because of its non-swelling characteristics.

Lactose, by its water-soluble and hydrophilic nature, facilitates gel formation and shortens the penetration time of the dissolution medium into the matrix. Moreover, this soluble substance acts as a channeling agent by rapidly dissolving and easily diffusing outward, therefore decreasing tortuosity and/or increasing the matrix porosity. On the contrary, Dicalcium phosphate is a water-insoluble excipient which caused less prominent swelling, erosion, and drug release in matrices compared to lactose[13].

CONCLUSION

The study was designed to have combination therapy of Diltiazem HCl and Quercetin dihydrate for Angina pain. In culmination of study various formulation parameter were studied during formulation of immediate release pellets. It was found that F16 formulation containing Crospovidone as a superdisintegrant and Lactose as a diluent in presence of Surfactant showed minimum Disintegration time of 9min and 100% drug release of Diltiazem HCl and Quercetin dihydrate respectively with 710µm pellets size. Hence it was concluded that the immediate release pellets can be considered as a promising approach for Diltiazem HCl and cardio protective Quercetin dihydrate for combination therapy.

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