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Original Article

Formulation, optmization and evaluation of taste masked oral disintegrating tablet of verapamil HCL

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ABSTRACT

Verapamil HCl is calcium channel blocker used for the treatment of hypertension, irregular heartbeat, angina, and to control the systolic and diastolic blood pressure. As Verapamil HCl is bitter in taste, taste masking is required for preparing oral disintegrating tablet. To mask the taste we used resin Indion 234. Oral disintegrating Tablets were made using various superdisintegrants (crosspovidone, SSG, Kyron T 314) at 3 different concentration with three different ratio (Drug: Indion 234) 1:1, 1:2, 1:3 of drug and resin equivalent to 40mg form a Drug Resin complex (DRC). Crosspovidone shows the best disintegration time and it is further used for the formulation of the tablets. All the formulations were evaluated for parameters such as hardness, friability, disintegration time, *in vitro* drug release. An effective formulation F8 having hardness 4.1 kg/cm^2 , disintegration time of 21sec. and *in vitro* drug release of 98.87% after 20min. The bitterness scale 0.6 confirmed by study on human volunteers. The taste masking of the drug confirmed by FTIR, DSC study and the *in vitro* release of the DRC

Key word: Oral Disintegrating Tablet, Superdisintegrants, Indion 234, Drug Resin complex.

INTRODUCTION

Hypertension is according to WHO it is the state of body in which systolic blood pressure is 150 mmHg and diastolic blood pressure is 95 mmHg or more. Hypertension is usually defined by the presence of a chronic elevation of systemic arterial pressure above a certain threshold value.[1] However, increasing evidence indicates that the cardiovascular (CV) risk associated with elevation of blood pressure (BP) above approximately 115 ⁄ 75 mm Hg arises in a log-linear fashion. Hypertension is a progressive CV syndrome. Early symptoms of the syndrome are often present before BP elevation is sustained; therefore, hypertension cannot be classified solely by discrete BP thresholds values. Progression is strongly associated with functional and structural cardiac and vascular abnormalities that damage the heart, kidneys, brain, vasculature, and other organs and lead to premature morbidity and death also. Decrease in BP when target organ damage is demonstrable or the functional precursor of target organ damage is present and still reversible generally reduces the risk for CV disease. Calcium channel blockers are the type of drugs which are used to treat the elevated blood pressure. They act by slowing the movement of the calcium ion in to the smooth muscle of the heart and blood vessel walls which makes comfortable for the blood vessel to pump out the blood easily the result is that heart dosen't have to work hard and it lowers the blood pressure. Calcium channel blocker have added benefit that slowing the heart rate which can further reduce blood pressure and reduces the chest pain.[2,3,4]

Verapamil hydrochloride is a calcium ion influx inhibitor (slow-channel blocker or calcium ion antagonist) that exerts its pharmacologic effects by modulating the influx of ionic calcium across the cell membrane of the arterial smooth muscle. Calcium channel blocker binding to L-type calcium channel and reducing calcium flux. Here muscle does not respond calcium ion signal, Relaxes smooth muscle of heart and slow down the elevated blood pressure. Long-acting medications are slowly released and helpful to provide a longer lasting

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effect. Calcium channel blockers reduces the blood pressure by limiting the amount of calcium. Calcium stimulate the heart to contract forcefully, so when the entry of calcium is limited the blood vessel are able to relax and it will lowers and controls the heart rate.[5,6,7] Calcium channel blocker are available in many number of oral dosage form. Ranging from short acting dissolving tablets to extended release tablets and capsules. Dosage of the drug varies according to the overall health and medical history. The age of person is also very much important for the application of the calcium channel blocker. In recent development in oral dosage form oral disintegrating tablet offers major advantage for fast action. The main objective of the present study is to formulate and evaluate taste masked ODT for better patient compliance and faster action as compare to conventional tablets.[8]

MATERIALS AND METHOD

Materials: Verapamil HCl was obtained from kivi laboratories, Vadodara, Crosspovidone, Kyron t 314, Indion 234, Avicel pH 101 was purchased from chemdyes corporation, Mannitol, Sodium starch glycolate and Talc purchased from suvidhinath laboratories, Aspartame and Magnesium stearate was purchased from loba chemie.

Methods

Formation of Drug Resin complex (DRC): The Drug: resin (Indion 234) ratio was prepared with three different ratio. (1:1, 1:2, 1:3) The drug resin complex (DRC) was prepared by adsorption method. Initially the accurate required amount of drug was taken. Dissolved the drug in highly volatile solvent, here we used methanol. After that resin was added as per the drug:resin (Indion 234) ratio. Solvent was evaporated at the room temperature and the mixture was dried at room temperature. As the resin is insoluble in solvent it forms the complex with the drug molecule at the particular binding site. [9,10]

Drug Resin Complexation study: The DSC curves of verapamil HCl, indion resin and drug resin complex was taken. The melting point of drug and change in crystalline to amorphous form was observed. The FTIR spectra of drug only, Indion 234 only and drug resin complex (DRC) was taken and change in peaks of binding site in drug and resin FTIR was observed at particular wavenumber.[10,11]

Drug Resin *in vitro* release study: The three different ratio of drug-resin complex (1:1,1:2,1:3) was evaluated for the drug release study at phosphate buffer pH 6.8 and the release was observed for the conformation weather the complex is formed and release is controlled at salivary pH or not.[12]

Preparation of ODTs: The tablets were prepared by direct compression method. The DRC equivalent to 40mg of drug was taken. Accurately weighed all the ingredient with screened superdisintegrant on the basis of disintegration time was taken, after that the blend was passed from sieve no 60. The above blend was compressed using 7mm round standard concave tooling on a rotary compression machine (Rimek karnavati mini plus)

Evaluation of Orally Disintegrating Tablets
Evaluation of powder blend: The core powder blend was evaluated for angle of repose, carr's index, hausner's ratio, tapped density and bulk density.

***In vitro* disintegration time:** The *in-vitro* disintegration time was determined by disintegration test apparatus. The time for disintegration of tablets is generally <1 min & actual disintegration time that patient can experience ranges from 5 to 30 s. A tablet is placed in each of the six tubes of the apparatus, & one disc is added to each tube & measure the disintegration time when all tablets get breaks in to smaller particles.

Wetting time: Wetting time of tablet is related with the contact angle. The wetting time of Oral Disintegrating tablets is important parameter, which needs to be assessed to give the disintegration properties of the tablets. A lower wetting time of tablet gives a faster disintegration of the tablet. Wetting time of the tablet can be measured using a simple process. Five circular tissue papers of 10 cm diameter were placed in a petri dish with a 10 cm diameter. Ten ml of water containing Amaranth, a water soluble dye was added to petri dish. A tablet was carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet was noted as wetting time.[13]

***In vitro* drug release study:** It is an important test as the drug-release profile can be obtained by performing this test. Dissolution of oral disintegrating tablet is very rapid. USP 2 paddle-type apparatus at 100 rpm was used for dissolution testing, using 900 ml 0.1N HCl at 37 ± 0.5°C as dissolution media. Aliquots of 5 ml of dissolution medium were withdrawn at specific time intervals (2, 5,10,15,20 minutes etc), filtered & the amount

of drug released was determined by UV Spectrometer at λ max 278 nm. Perform it for all the nine formulations.

Taste masking evaluation: Testing was done by taking the sample (1 Tablet) into the mouth, placing it into oral cavity for approximately 15 seconds without swallowing (the tablet or saliva), and then spitting it out. Immediately after tasting each tablet, participants will score the treatments for taste on the basis of the conventional tablet given as a standard initially for the same period, (0=good, 1=tasteless, 2=slightly bitter, 3=bitter, 4=very bitter, 5=awful) Participants will be permitted to select a score, between the minimum score of 0 and the maximum score of 5. The higher the score, the greater the bitterness.

RESULT AND DISCUSSION

The DSC curves of verapamil HCl, Indion 234 and the DRC was observed. The pure drug has distinct melting peak at 146.15ºC which corresponded to the intrinsic melting point. However no characteristic melting point was observed in the DSC thermogram of the DRC. Suggesting that the drug was changed from crystal structure to the amorphous form due to the resin presented as carrier. Fig 1,2,3 The comparative FTIR spectra of Verapamil HCl, Indion 234 and drug resin complex (DRC) are shown in fig 4-7. Initially the change in the IR spectra of the resin was observed. Fig 4 shows the IR spectra of resin Indion 234 only & figure 5 shows the drug-resin complex spectra. From the both spectra it was shown that in the spectra of resin the –COOH peak is broad but in the the spectra of complex the peak is sharp due to attachment of cyano group to –COOH. It confirms the attachment of the cyano group and adsorption of the drug on resin. The change in the IR spectra of drug was observed. In the IR spectra of the drug the peak of cyano group was there at 2236.79 cm−1 but in the complex with the resin the peak was disappear and it was shown in the IR spectra of Indion 234. It confirms the adsorption of the drug on the indion resin which acts as a carrier for the drug molecule. Fig 6,7

In vitro disintegration time study was carried out and it was observed that the crosspovidone having less disintegration time 20±0.577 sec from all three superdisintegrant. The disintegration time of all nine batches was observed in which crosspovidone was used. The F8 batch shows best disintegration time 21±1 sec. The Wetting time is an important parameter to evaluate the swelling behavior of ODTs. The wetting time for each formulation ranges from 55 to 69 sec. It was observed that the tablet with the highest concentration of the crosspovidone having less wetting time 55±1 sec. The results of F1 to F9 are shown in table 23,4 Figure 9,10,11show the plot of % *in vitro* drug release Vs time. The optimized formulation gave minimum disintegration time, disintegration time of 21± 1 seconds & *in vitro* drug release of 98.87 ± 0.75% within 20 minutes. The taste masking evaluation on human volunteers was done. The result are evaluated on the basis of the score given by panel of 10 healthy human volunteers. It was observed that average score of panel was given 0.6. it indicates that the formulation was good and tasteless.[15]

Conclusion

The Oral Disintegrating tablet of Verapamil HCl was prepared by direct compression which shows acceptable pre-compression properties, post compression properties. The optimized formulation gives minimum disintegration time of 21±1 sec. and *in vitro* drug release of 98.87±0.75 % after 20 min with compare to marketed product it is 17.48 ± 0.53 % , it shows better drug release at stomach pH. It was observed that the drug release at the salivary pH 6.8 was very low between 10% to 13% of all three ratio of drug resin complex after 20 min so it confirms that taste masking was achieved and less bitterness felt by the patient. The result of the stability study for 1 month indicates that tablet is relatively stable upon storage. Thus it can be concluded that tablet can be used for effective management in hypertensive condition with better patient compliance.

Table 1: formula for oral disintegrating tablet of Verapamil HCl

Ingredients(mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Drug resin complex eq. to 40mg of Verapamil HCl	80	120	160	80	120	160	80	120	160
Crosspovidone	4	4	4	8	8	8	12	12	12
Avicel pH 102	80	80	80	80	80	80	80	80	80
Mannitol	156	116	76	152	112	72	148	108	68
Aspartame	10	10	10	10	10	10	10	10	10
Pippermint flavour	10	10	10	10	10	10	10	10	10
Mg. Stearate	6	6	6	6	6	6	6	6	6
Talc	4	4	4	4	4	4	4	4	4
Total wt.(mg)	350	350	350	350	350	350	350	350	350

Table 2: Evaluation of powder blend (F1 to F9)

Batch no.	**Angle of repose (°) ± SD, N=3**	**Bulk density(g/ml) ± SD, N=3**	**Tapped density(g/ml) ± SD, N=3**	**Carr's index (%) ± SD, N=3**	**Hausner's Ratio ± SD, N=3**
F1	33.36±0.577	0.635±0.001	0.73±0.02	11.43±1.12	1.14±0.035
F2	33.33±1.527	0.631±0.001	0.723±0.002	13.41±0.88	1.14±0.005
F3	35±1	0.638±0.0015	0.6±0.12	14.08±1.48	1.15±0.01
F4	35±0.577	0.637±0.0005	0.766±0.029	13.78±1.06	0.93±0.18
F5	36.33±1.527	0.637±0.0025	0.755±0.003	14.50±1.37	1.20±0.011
F6	34.33±0.577	0.641±0.001	0.766±0.01	13.61±1.00	1.18±0.04
F7	35.66±0.577	0.635±0.0005	0.755±0.003	13.24±2.14	1.18±0.005
F8	35.66±1.52	0.635±0.001	0.729±0.0015	13.08±1.44	1.14±0.005
F9	32±0.577	0.638±0.005	0.784±0.005	16.73±1.41	1.22±0.015

Table 3: *in vitro* disintegrating time and wetting time

Batch no	Disintegration time(sec) ± SD, N=3	Wetting time(sec) ± SD, N=3
F1	30.3±0.577	69.6±0.577
F2	29.3±0.577	67.6±0.577
F3	31±2.08	67.6±1.52
F4	26.6±1.52	63±1
F5	24.3±1.52	60.6±0.577
F6	25.3±1	60±1
F7	22±1.52	57.6±1.52
F8	21±1	56.6±1.52
F9	21.3±1	55±1

Table 4: drug release profile of formulation F1 to F9

Time(min)	F1± S.D N=3	F2± S.D N=3	F3± S.D N=3	F4± S.D N=3	F5± S.D N=3	F6± S.D N=3	F7± S.D N=3	F8± S.D N=3	F9± S.D N=3
2	**33.74± 1.12**	**36.20 ±2.81**	**33.76 ±1.74**	**48.57 ±1.20**	**38.06 ±1.53**	**45.65 ±1.54**	**45.44 ±1.88**	**41.6 ±1.63**	**41.81 ±1.47**
5	**44.42 ±0.83**	**47.54 ±1.50**	**54.83 ±2.08**	**66.90 ±1.42**	**61.64 ±1.37**	**63.70 ±1.35**	**67.12 ±1.68**	**67.53 ±1.0**	**52.71 ±1.41**
10	**66.80 ±1.88**	**72 ±2.79**	**66.74 ±1.53**	**86.05 ±1.64**	**69.34 ±1.04**	**72.23 ±1.56**	**76.42 ±2.49**	**74.27 ±1.66**	**75.41 ±0.79**
15	**84.81 ±2.24**	**85.59 ±1.31**	**80.93 ±1.44**	**92.11 ±1.71**	**82.23 ±1.06**	**91.44 ±0.87**	**90.85 ±0.49**	**90.82 ±0.43**	**85.50 ±0.88**
20	**91.57 ±1.64**	**93.96 ±1.84**	**94.77 ±0.92**	**95.15 ±0.54**	**96.76 ±0.65**	**97.91 ±0.93**	**97.46 ±1.35**	**98.87 ±0.75**	**98.34 ±0.91**

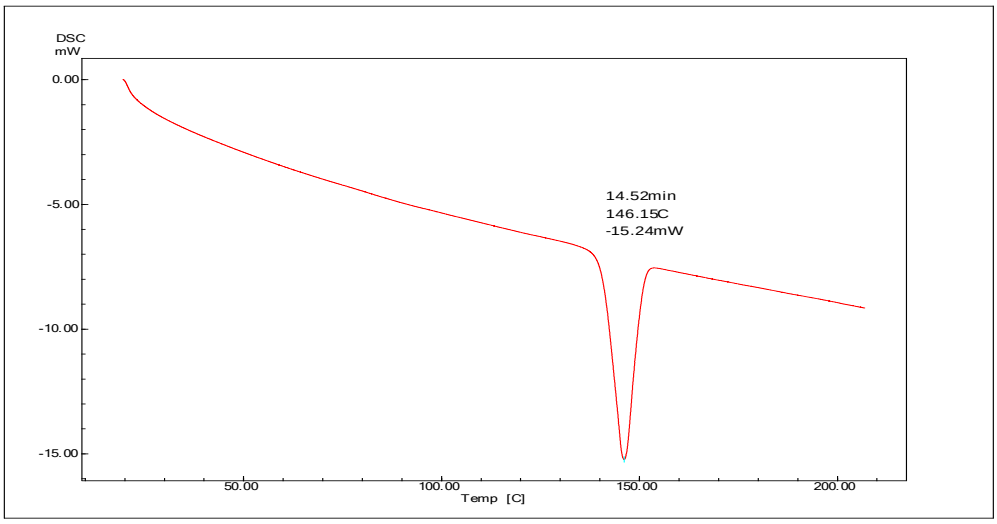

Figure 1 DSC of verapamil HCl

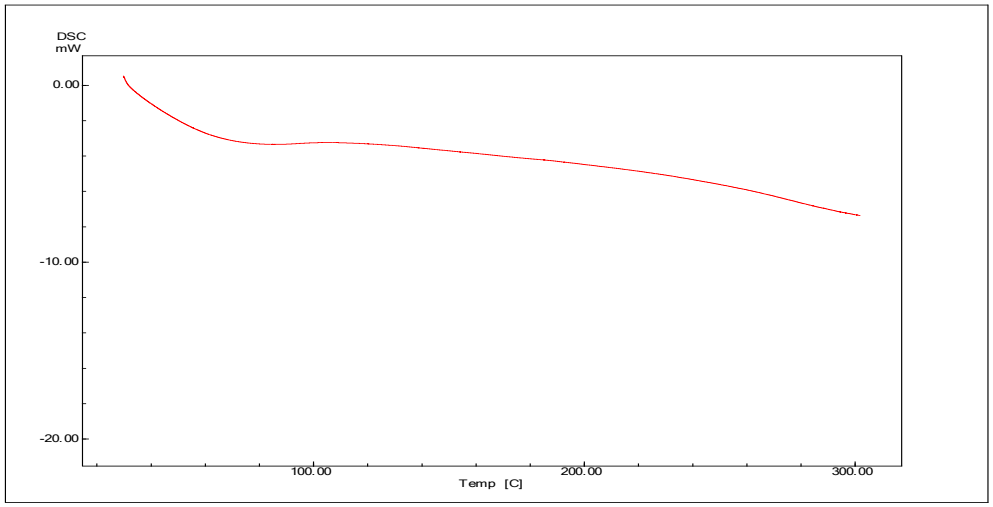

Figure 2 DSC of Indion 234

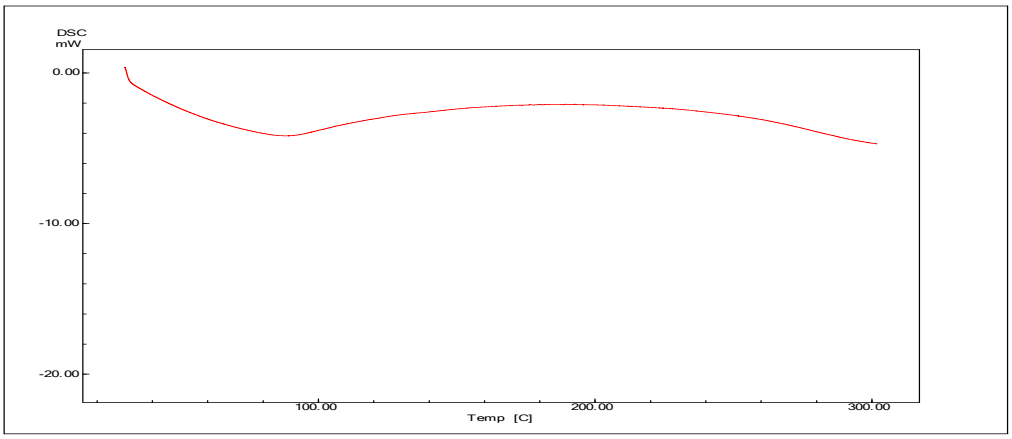

Figure 3 DSC of drug+ resin complex

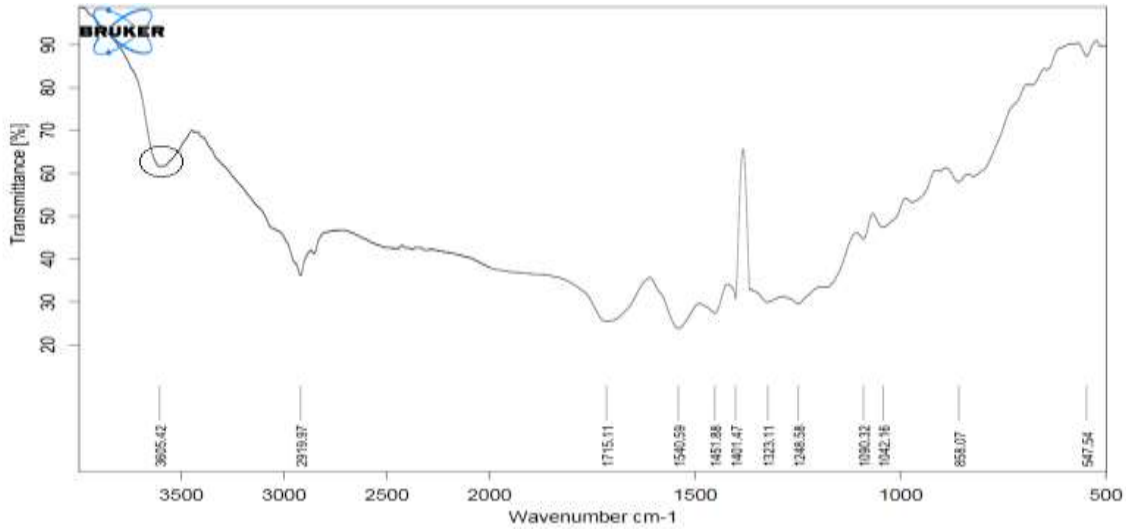

Figure 4 IR spectra of Indion 234

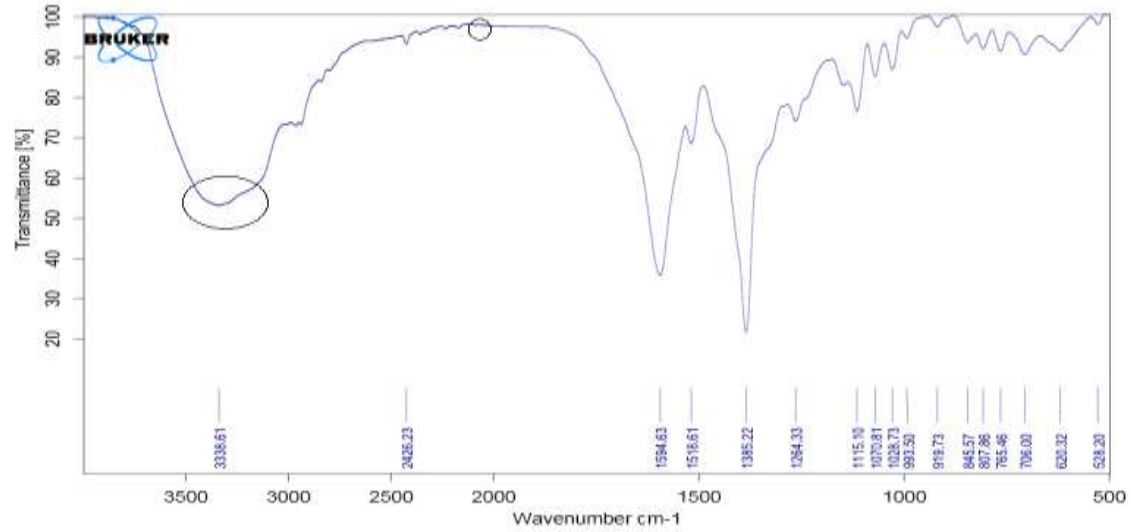

Figure 5 IR spectra of drug + resin

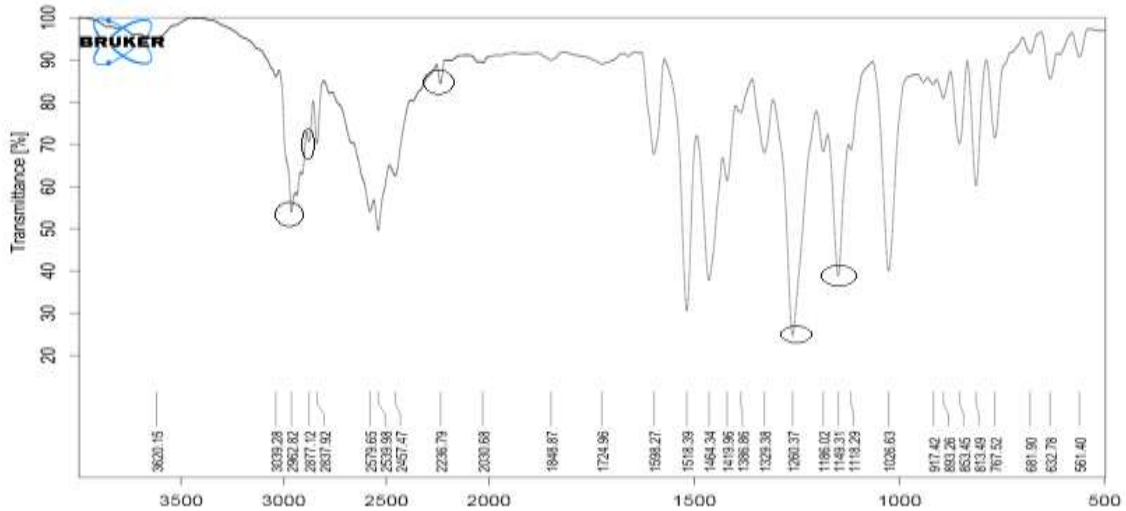

Figure 6 IR spectra of Verapamil HCl

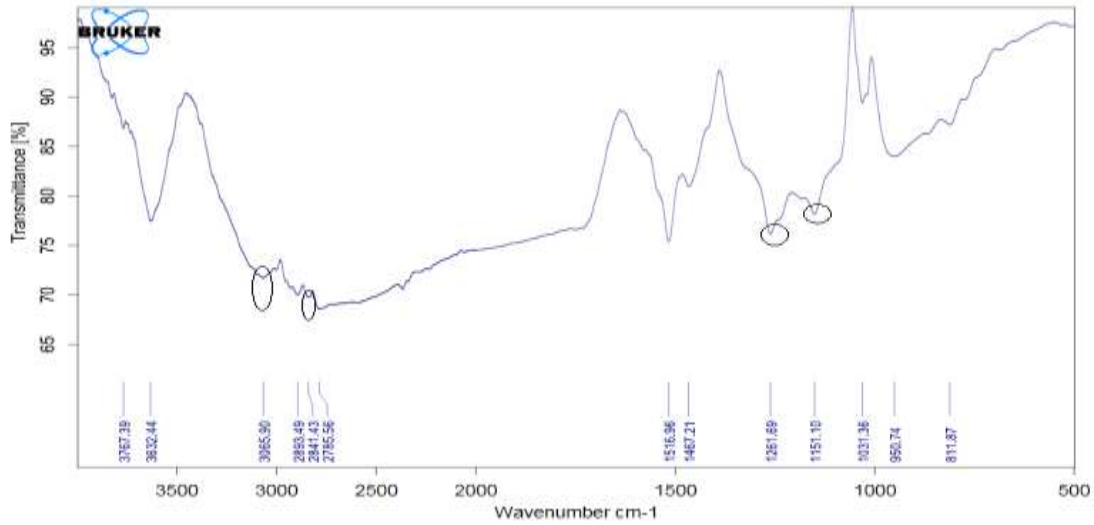

Figure 7 IR spectra of drug resin complex

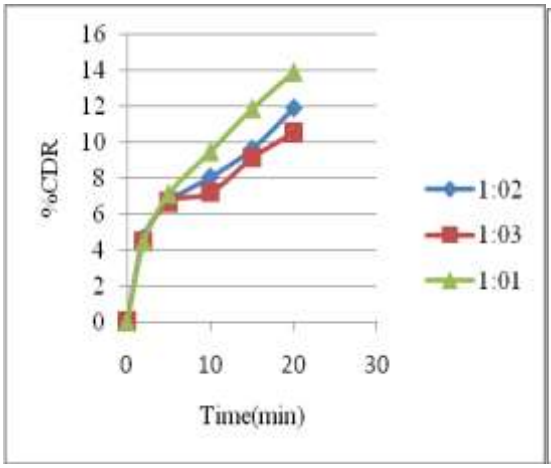

Figure 8 Drug release from DRC at pH 6.

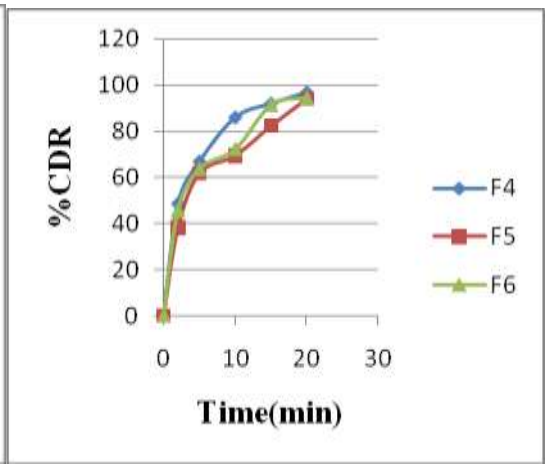

figure 9:% CDR F4 to F6 batch(0.1N HCl)

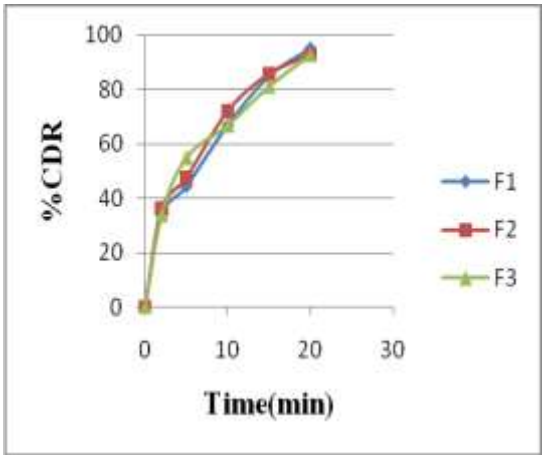

Figure 10:% CDR F1 to F3 batch(0.1N HCl)

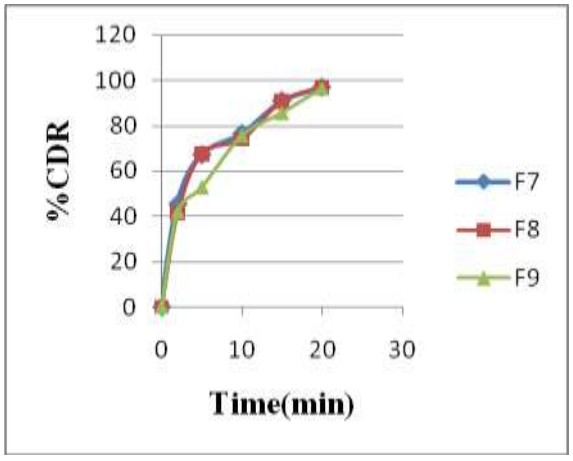

Figure 11: % CDR F7 to F9 batch(0.1 N HCl)

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