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Formulation and Development of Diltiazem HCL Controlled Released Microcapsules by Ionotropic Gelation Technique

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ABSTRACT

The aim of the present study was to prepare and evaluate microcapsules of Diltiazem Hydrochloride using blend of Sodium CMC and Xanthan Gum by Ionotropic Gelation technique for controlled release. Microscopic analysis data indicated that the prepared microcapsules were in the ranges of 1009 to 1311µm. SEM photographs confirm the prepared formulations are spherical in nature. DSC studies and FT IR spectra showed that the encapsulated drug was stable in the prepared formulations. The prepared formulations were analyzed quantitatively for the amount of encapsulated drug. From the drug loading, encapsulation efficiency and in vitro drug release data, optimum formulation F7 was selected. The optimum formulation shows the drug release of 84.04% up to 12 h having drug loading and encapsulation efficiency of 18.24 mg and 91.20% respectively. It was also observed that, there was no significant release of drug at gastric pH. The release kinetics for all the formulations indicated that drug release followed non -Fickian diffusion. The optimized formulation was selected for stability studies. The release performance was greatly affected by the ratio of materials used in preparation of microparticles. Diltiazem Hydrochloride loaded microcapsules have desirable release profiles and worthy of further investigation as an oral controlled release dosage form.

Keywords: Diltiazem Hydrochloride; Microparticles; controlled release; Ionotropic.

INTRODUCTION

Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects. In addition, the oral medication is generally considered as the first avenue investigated in the discovery and development of new drug entities and pharmaceutical formulations, mainly because of patient acceptance, convenience, and cost effective manufacturing process[1].

It is an established fact that the conventional immediate release drug delivery systems when taken frequently in a day can maintain drug concentration levels in therapeutically effective range. The new way of patenting the drug is to use "**Novel Drug Delivery Systems**" i.e. NDDS with improved bioavailability (BA). To formulate a drug or to re-formulate it in a form of NDDS is not a Herculean task if one goes methodically and skillfully. This is where the formulation development studies play an important role[2].

Drug absorption at the desired rate means, first to reach the effective plasma level within an acceptable short time period; second, to avoid an overshoot in the case of rapidly absorbed drugs and third to maintain effective plasma levels over the desired time period. Although the intensity of pharmacological effect is related to the drug concentration at the site of action, which is in turn, related to the plasma drug concentration, an ideal situation is obtained when the concentration is continuously maintained between minimum effective and maximum safe levels (Therapeutic Index). Invariably, conventional drug dosage forms do not maintain the drug[3].

Modified release DDS, in general, can broadly divided into four categories:

Delayed release
Site specific release
Receptor release
Sustained release

Hypertensive is defined as an abnormal elevation in diastolic pressureand/or systolic pressure; mean arterial pressure is also elevated in hypertension, but it is not usually measured in people.

Controlled drug delivery containing polymeric carriers has gained increased interest in last two decades, because they can be fabricated into films, rods .and microparticles[16].

A microparticle" may be defined as a spherical particle with size varying from 1 to 1000µm containing a core substance[4].

Microencapsulation is a process of applying relatively thin coatings to small particles of solids or droplets of liquid containing one or more drugs and dispersions.

Reasons for Microencapsulation:

- Sustained and prolonged release of drugs.
- Masking of unacceptable taste or odour of drugs.
- Preparation of free flowing powders from drugs in liquid form.
- Stabilization of drugs sensitive to oxygen, moisture or light.
- Elimination of incompatibilities among drugs.
- Prevention of vaporization of volatile drugs.
- Reduction of toxicity and to reduce gastro-intestinal irritation.
- Alteration in site of absorption.

Microparticles are encapsulated particles between 1 and 1000 µm in size. The uniqueness of microencapsulation is the smallness of coated particles and their subsequent use and adaptation to a wide

variety of dosage forms and product applications.

Controlled drug release from microparticles occurs by

1. Diffusion of drug through polymeric excipients,
2. Diffusion of entrapped drug as the polymer erodes, and
3. Release of drug through pores in the polymeric membrane.

If the drug is released by diffusion through the polymer without erosion, the release depends on the surface area of the microparticles and the path length followed by the drug in transit to the surrounding environment[5].

Ionotropic gelation is based on the ability of polyelectrolytes to cross link in the presence of counter ions to form hydrogels. Since, the use of alginates, gellan gum, chitosan, and carboxymethyl cellulose for the encapsulation of drug and even cells, ionotropic gelation technique has been widely used for this purpose. It is generally understood that the release of drug from microcapsules/beads can be considered as mass transport phenomenon involving the diffusion of drug molecules from higher concentration in the dosage form to a region of lower concentration in the surrounding environment[6].

MATERIALS AND METHODS

Preparation of Diltiazem Hydrochloride microcapsules

An accurately weighed quantity of Diltiazem Hydrochloride was dispersed in an aqueous solution of carboxymethyl cellulose sodium (NaCMC) and Xanthan gum and mixed homogeneously using magnetic stirrer. Twenty milliliters of dispersion was extruded in the form of droplets into 100 ml aqueous solution of AlCl3 solution using 25 ml hypodermic syringe through a needle (number 23). The beads were removed after the defined gelation period and washed with distilled water repeatedly to make free from un-reacted ions and dried at room temperature for 24 h and then at 40◦C for 10 h[7].

Characterization of Microparticles:

Particle size analysis[8]

The particle size of the prepared microbeads was measured by using a digimatic micrometer (MDC-255 Mitutoyo, Tokyo, Japan) having an accuracy of 0.001 mm. the average diameter of the 100 particles per batch was calculated.

Scanning Electron Microscopic (SEM) studies[9]

SEM photographs were taken with a scanning electron microscope Model Joel-LV-5600, USA, at the required magnification at room temperature. The photographs were observed for morphological characteristics and to confirm spherical nature of the microparticles.

Fourier Transform Infrared Spectroscopic (FT IR) studies[10]

FTIR analysis was carried out for pure drug and for microparticles with and without drug using KBr pellet method on FTIR spectrophotometer .Drug was mixed with KBr and spectra was taken. FT-IR spectrum of pure drug Diltiazem HCl was compared with FT-IR spectra of Diltiazem HCl formulations. Disappearance of peaks or shifting of peaks in any of the spectra was studied using the apparatus FTIR- 8400-S, Shimadzu, Japan.

Differential Scanning Calorimetry (DSC)[11]

DSC is a technique in which the difference in heat flow between the sample and a reference is recorded versus temperature All dynamic DSC studies were carried out on Mettler Toledo thermal analyzer with 2010 DSC module. Calorimetric measurements were made with empty cell as the reference. The instrument

was calibrated using high purity indium metal as standard. The dynamic scans were taken in nitrogen atmosphere at the heating rate of 10º c/min. The runs were made in triplicate. The scanning temperature for reference pure drug and formulation are the same when dynamic measurements are performed, and hence the required heat energy for chemical transformation is directly recorded on a heat flow versus temperature graph. The energy is measured as Joules per kilocalorie.

X- Ray Diffraction Studies (XRD)[12]

The spectra were recorded using a P Analytical X' Pert pro, x-ray diffractometer with Cu-Nf filtered CuKα radiation. Quartz was used an internal standard for calibration. The powder x-ray diffractometer was attached to a digital graphical assembly and computer with Cu-Nf 40 KV/30 mA tube as a CuKα radiation source in the 2θ range 0-50ºC.

Drug loading and encapsulation efficiency[13]

Drug loading is important with regard to release characteristics. Generally, increased drug loading leads to an acceleration of the drug release. Drug entrapment efficiency represents the proportion of the initial amount of drug, which has been incorporated into the microparticles. 100 mg of Diltiazem HCl microparticles were weighed and transferred to 100 ml volumetric flask containing pH 7.4 phosphate buffer. From this, 1 ml of solution was transferred to 10 ml volumetric flask and diluted up to the mark. Further 1 ml of this solution is diluted to 10 ml and absorbance was measured at 236 nm. The drug content was calculated by using the formula.

$$\text{Amount of drug} = \frac{\text{Conc. from standard graph} \times \text{dilution factor}}{1000}$$

Percentage encapsulation efficiency is found out by calculating the amount of drug present in 100 mg of microparticles.

In vitro drug release studies[14]

The in vitro release of drug from the microparticles was carried out in basket type dissolution tester USP XXIII, TDT-08L, with auto sampler containing 900 ml of pH 1.2 buffer for the first 2 hrs and in 7.4 pH phosphate buffer for the next 22 hrs. The volume of the dissolution media was maintained at 900 ml with constant stirring (100rpm) and temperature of bath was maintained at 37 ± 0.5°C. Aliquots (10 ml) of dissolution media were sampled at specified time points and replaced with fresh media immediately after sampling. Samples were analyzed for drug content by UV Visible spectroscopy .The release data obtained were fitted into various mathematical models to know which mathematical model is best fitting for the obtained release profile. Dissolution studies were carried out for all the batches of the prepared formulations (09 batches).

DISCUSSION

The microcapsules of Xanthan gum and Sodium CMC containing diltiazem HCl were prepared by ionotropic gelation method using Aluminium chloride. The obtained microcapsules were spherical in shape and freely flowing. The surface morphology was examined by scanning electron microscopy studies (SEM). The SEM microphotographs of microcapsules showed that the prepared microcapsules are spherical, having rough surface without surface foldings.

FT IR spectra were obtained for Diltiazem HCl pure drug and Diltiazem HCl loaded microcapsules from the data it is observed that a similar characteristic peak of Diltiazem Hydrochloride and Formulation F7 were appeared with minor differences. The characteristics peaks found both in pure drug of Diltiazem and formulation F7, hence it appears there is chemical interaction between drug and polymer and it can be concluded that

the characteristics bands of pure drugs were not affected after successful loading.

The DSC analysis of plain diltiazem, drug-free beads and drug-loaded beads was carried out. The drug-free beads have shown an endothermic peak at 117oC and 180 ◦C indicating melting temperature of the polymer, whereas drug-loaded beads showed an endothermic peak at 121oC. The plain diltiazem has shown a sharp endothermic peak at 215oC due to melting of the drug, but this peak is not seen in the drug-loaded beads. This indicates that the drug was molecularly dispersed in an amorphous state in the polymer matrix.

The X-ray diffractograms of diltiazem, drug free beads and drug-loaded beads are carried out. Diltiazem has shown characteristic intense peaks between the 2 of 8^o and 16^o due to its crystalline nature. Whereas, in case of drug loaded beads, no intense peaks related to drug were noticed between the 2 of 8^o and 16^o. This indicates the amorphous dispersion of the drug after entrapment into beads.

The *in-vitro* drug release study was performed using dissolution rate test apparatus in 0.1 N HCl (pH 1.2) and phosphate buffer (pH 7.4). The results indicate that the beads were capable of releasing drug up to 9 hours. The 96.96, 93.53, 90.18, 86.68, 84.28, 88.57 and 85.75 drug was released from F1, F2, F3, F4, F5, F8 and F9 beads at the end of 9th hour, while 89.52 and 84.04% drug was released from the crosslinked F6 and F7 beads respectively at the end of 12th hour. The beads which were prepared with higher concentration of AlCl3 released the drug more slowly. Also increase in concentration of the polymer resulted in decreased drug release. The increase in initial drug loading increased the drug release.

The stability study was performed for the prepared formulation as per the ICH guidelines and it showed that the formulation F7 was stable, with no physical change and also there was no significant reduction in drug content.

CONCLUSION

From the FT-IR spectra, it was observed that similar characteristic peaks appear with minor differences for the drug and their formulations. Hence, it appears that there was no chemical interaction between the drug and the polymer used.

The DSC thermogram obtained for the pure drug, drug free beads and for the formulation shows that the drug was uniformly dispersed in an amorphous state in the polymer matrix.

The SEM studies clearly showed that the obtained microcapsules exhibited good spherical nature.

The XRD studies are useful to investigate the crystallinity of the drugs after entrapment into the dosage forms; the x-ray diffraction studies indicated the amorphous dispersion of the drug after entrapment into beads.

From the results of drug content determination, it can be inferred that there was a proper and uniform distribution of drug in the microcapsules prepared by Ionic Gelation method. The percentage encapsulation efficiency also showed that the drug loading is optimum.

The in vitro drug release indicated that the beads which were prepared with higher concentration of Aluminium chloride released the drug more slowly. Also increase in concentration of the polymer resulted in decreased drug release. The increase in initial drug loading increased the drug release. Drug release mechanism followed non-Fickian transport.

From the results of the present experimental work, it can be concluded that the microcapsules formulation is easy to administer, simple, comfortable, with increased patient compliance. Hence it is

stated that Diltiazem Hydrochloride could be formulated into microcapsules as controlled drug release dosage form.

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Table 1. Microencapsulation processes & their applicabilities

Microencapsulation Processes & their Applicabilities Microencapsulation process	Applicable core material	Approximate particle size (µm)
Air suspension	Solids	35-5000
Coacervation-phase separation	Solids & liquids	2-5000
Multiorifice centrifugal	Solids & liquids	1-5000
Pan coating	Solids	600-5000
Solvent evaporation	Solids & liquids	5-5000
Spray drying and congealing	Solids & liquids	600

Table 2. List of materials

MATERIALS	SOURCE
Diltiazem Hydrochloride	Shrushti Pharmaceuticals, Bangalore
Sodium CMC	SD Fine chemicals Ltd., Mumbai
Xanthan Gum	Kachabo Gums., Mumbai
Aluminium Chloride Hexahydrate	Thomas Baker Chemicals Ltd, New Delhi
Potassium chloride	Loba Chemie Pvt Ltd, Mumbai
Hydrochloric acid	SD Fine chemicals, Mumbai
Sodium hydroxide pellets	SD Fine chemicals, Mumbai
Potassium dihydrogen orthophosphate	SD Fine chemicals, Mumbai

Table 3. List of equipments and instruments

EQUIPMENT	MODEL/ MANUFACTURER
Magnetic stirrer	Remi motors, Mumbai
Digital balance	Adair dutt instrument pvt. Ltd.
Hot air oven	Tempo, Mumbai
Dissolution apparatus (6 basket)	Lab India, LTD Mumbai, India.
UV – Visible spectrophotometer	Shimadzu-1700, Japan
FT-IR spectrophotometer	8400S, Shimadzu, Japan
Scanning electron microscope	JEOL, JSM-6360, Kyoto, Japan

Table 4. Formulation code of Diltiazem hydrochloride loaded microcapsules

Formulation codes	Xanthan gum (% w/v)	Sodium CMC (% w/v)	Aluminium chloride Hexahydrate (%w/v)	Curing Time
F 1	2.0	1.0	5	10
F 2	1.5	1.5	5	10
F 3	1.0	2.0	5	10
F 4	1.5	1.5	10	10
F 5	1.5	1.5	15	10
F 6	1.5	1.5	20	10
F 7	1.5	1.5	20	10
F 8	1.5	1.5	10	15
F 9	1.5	1.5	10	20

Table 5. Dissolution media used for prepared formulation

S. No	Formulations	Quantity used	Dissolution media	
			For first 2 hrs	For next 10 hrs
1	F1-F9	Equivalent to 30 mg of Diltiazem Hydrochloride	pH 1.2 buffer	pH 7.4 phosphate buffer

Table 6. % Yield of Diltiazem Hydrochloride loaded microparticles

Formulation	% Yield ± SD*
F1	85.76 ± 1.24
F2	81.58 ± 1.84
F3	83.80 ± 1.43
F4	87.29 ± 1.63
F5	89.59± 1.33
F6	91.05 ± 1.21
F7	95.50± 1.63
F8	88.75± 1.82
F9	88.95 ± 1.38

***Standard deviation, n = 3

Table 7. Average bead size and drug entrapment efficiency (dee) of xanthan gum and Sodium CMC beads

Microbeads	Average size (□m)	DEE (%)
F1	1204□ 1.89	70.33□ 0.052
F2	1120 ± 1.45	74.26□ 0.085
F3	1064 ± 1.36	67.86□ 0.15
F4	1009 ± 2.36	77.13□ 0.45
F5	1311 ± 4.56	82.93□ 0.75
F6	1277 ± 1.87	86.67□ 0.45
F7	1259 ± 3.44	91.20□ 0.08
F8	1250 ± 1.75	85.80□ 0.42
F9	1246 ± 1.89	83.33□ 0.75

The values are average of three determinations. ± indicates SD values

Table 8. *In Vitro* release data of Diltiazem from F1

S. No	Time (Hrs.)	Square Root of time	Log time	% Drug release	% Drug remained	Log Percentage drug release	Log Percentage drug remain
1	0.0	0	0	0	0	0	0
2	0.5	0.70	-0.30103	15.76	84.28	1.197584	1.928498
3	1.0	1.00	0	34.26	65.74	1.534826	1.817829
4	1.5	1.22	0.17609	50.02	49.98	1.699179	1.698796
5	2.0	1.41	0.30103	64.41	35.59	1.808984	1.551327
6	3.0	1.73	0.47712	78.80	21.20	1.896554	1.326335
7	4.0	2.00	0.60206	86.68	13.32	1.937947	1.124504
8	5.0	2.23	0.69897	90.45	9.55	1.956430	0.980003
9	6.0	2.44	0.77815	92.85	7.51	1.967796	0.875639
10	7.0	2.64	0.84509	93.88	6.12	1.972577	0.786751
11	8.0	2.82	0.90309	95.59	4.41	1.980431	0.644438
12	9.0	3.00	0.95424	96.96	3.04	1.986613	0.482873

Table 9. *In Vitro* release data of Diltiazem from F2

S. No	Time (Hrs.)	Square Root of time	Log time	% Drug release	% Drug remained	Log Percentage drug release	Log Percentage drug remain
1	0.0	0	0	0	0	0	0
2	0.5	0.70	-0.30103	10.96	89.09	1.039976	1.949828
3	1.0	1.00	0	29.46	70.54	1.469325	1.848435
4	1.5	1.22	0.17609	45.22	54.78	1.655400	1.738622
5	2.0	1.41	0.30103	57.21	42.79	1.757543	1.631342
6	3.0	1.73	0.47712	74.00	26.00	1.869280	1.414973
7	4.0	2.00	0.60206	81.13	18.87	1.909208	1.275771
8	5.0	2.23	0.69897	85.34	14.66	1.931200	1.166133
9	6.0	2.44	0.77815	87.91	12.09	1.944083	1.082426
10	7.0	2.64	0.84509	90.18	9.82	1.955112	0.992111
11	8.0	2.82	0.90309	92.13	7.87	1.964417	0.895974
12	9.0	3.00	0.95424	93.53	4.47	1.970989	0.650307

Table 10. *In Vitro* release data of Diltiazem from F3

S. No	Time (Hrs.)	Square Root of time	Log time	% Drug release	% Drug remained	Log Percentage drug release	Log Percentage drug remain
1	0.0	0	0	0	0	0	0
2	0.5	0.70	-0.30103	9.59	90.41	0.981984	1.956216
3	1.0	1.00	0	27.41	72.59	1.437916	1.860876
4	1.5	1.22	0.17609	41.45	58.55	1.617611	1.767526
5	2.0	1.41	0.30103	52.42	47.58	1.719517	1.677424
6	3.0	1.73	0.47712	69.55	30.45	1.842322	1.483587
7	4.0	2.00	0.60206	75.72	24.28	1.879218	1.385248
8	5.0	2.23	0.69897	79.83	20.17	1.902182	1.304705
9	6.0	2.44	0.77815	82.91	17.09	1.918641	1.232742
10	7.0	2.64	0.84509	86.68	13.32	1.937947	1.124504
11	8.0	2.82	0.90309	88.39	11.61	1.946446	1.064832
12	9.0	3.00	0.95424	90.18	9.82	1.955112	0.992111

Table 11. *In Vitro* release data of Diltiazem from F4

S. No	Time (Hrs.)	Square Root of time	Log time	% Drug release	% Drug remained	Log Percentage drug release	Log Percentage drug remain
1	0.0	0	0	0	0	0	0
2	0.5	0.70	-0.30103	7.19	92.81	0.857045	1.967594
3	1.0	1.00	0	26.03	73.97	1.415640	1.869055
4	1.5	1.22	0.17609	38.37	61.63	1.584045	1.789792
5	2.0	1.41	0.30103	48.99	51.01	1.690163	1.707655
6	3.0	1.73	0.47712	66.26	33.74	1.821283	1.528145
7	4.0	2.00	0.60206	72.74	27.26	1.861776	1.435525
8	5.0	2.23	0.69897	76.40	23.60	1.883131	1.372912
9	6.0	2.44	0.77815	79.83	20.17	1.902182	1.304705
10	7.0	2.64	0.84509	83.94	16.06	1.923993	1.205745
11	8.0	2.82	0.90309	85.31	14.69	1.931026	1.167021
12	9.0	3.00	0.95424	86.68	13.32	1.937947	1.124504

Table 12. *In Vitro* release data of Diltiazem from F5

S. No	Time (Hrs.)	Square Root of time	Log time	% Drug release	% Drug remained	Log Percentage drug release	Log Percentage drug remain
1	0.0	0	0	0	0	0	0
2	0.5	0.70	-0.30103	6.68	93.32	0.824861	1.969974
3	1.0	1.00	0	22.27	77.73	1.347745	1.890588
4	1.5	1.22	0.17609	34.94	65.06	1.543322	1.813314
5	2.0	1.41	0.30103	45.22	54.78	1.655330	1.738622
6	3.0	1.73	0.47712	61.09	38.91	1.785978	1.590061
7	4.0	2.00	0.60206	68.86	31.14	1.838023	1.493318
8	5.0	2.23	0.69897	72.98	27.02	1.863206	1.431685
9	6.0	2.44	0.77815	76.92	23.08	1.886043	1.363255
10	7.0	2.64	0.84509	80.86	19.14	1.907739	1.281941
11	8.0	2.82	0.90309	83.08	16.92	1.919538	1.228400
12	9.0	3.00	0.95424	84.28	15.72	1.925762	1.196452

Table 13. *In Vitro* release data of Diltiazem from F6

S. No	Time (Hrs.)	Square Root of time	Log time	% Drug release	% Drug remained	Log Percentage drug release	Log Percentage drug remain
1	0.0	0	0	0	0	0	0
2	0.5	0.70	-0.30103	3.76	96.30	0.576219	1.984887
3	1.0	1.00	0	14.39	85.61	1.158076	1.943197
4	1.5	1.22	0.17609	28.78	71.22	1.459106	1.886772
5	2.0	1.41	0.30103	38.13	61.87	1.581322	1.822102
6	3.0	1.73	0.47712	51.7	48.30	1.713516	1.722798
7	4.0	2.00	0.60206	62.05	37.95	1.792745	1.631342
8	5.0	2.23	0.69897	68.83	31.17	1.837806	1.560384
9	6.0	2.44	0.77815	73.04	26.96	1.863614	1.493318
10	7.0	2.64	0.84509	76.61	23.39	1.884298	1.447932
11	8.0	2.82	0.90309	78.8	21.20	1.896554	1.397940
12	9.0	3.00	0.95424	81.44	18.56	1.910856	1.350829
13	10.0	3.16	1	84.35	15.56	1.926115	1.304705
14	11.0	3.31	1.041393	86.95	13.05	1.939318	1.249687
15	12.0	3.46	1.079181	89.52	10.48	1.951966	1.203032

Table 14. *In Vitro* release data of Diltiazem from F7

S. No	Time (Hrs.)	Square Root of time	Log time	% Drug release	% Drug remained	Log Percentage drug release	Log Percentage drug remain
1	0.0	0	0	0	0	0	0
2	0.5	0.70	-0.30103	3.42	96.58	0.534826	1.984887
3	1.0	1.00	0	12.26	87.74	1.088709	1.943197
4	1.5	1.22	0.17609	22.95	77.05	1.360901	1.886772
5	2.0	1.41	0.30103	33.61	66.39	1.526496	1.822102
6	3.0	1.73	0.47712	47.18	52.82	1.673760	1.722798
7	4.0	2.00	0.60206	57.21	42.79	1.757543	1.631342
8	5.0	2.23	0.69897	63.66	36.34	1.803872	1.560384
9	6.0	2.44	0.77815	68.86	31.14	1.838023	1.493318
10	7.0	2.64	0.84509	71.95	28.05	1.857046	1.447932
11	8.0	2.82	0.90309	75.00	25.00	1.875072	1.397940
12	9.0	3.00	0.95424	77.57	22.43	1.889703	1.350829
13	10.0	3.16	1	79.83	20.17	1.902182	1.304705
14	11.0	3.31	1.041393	82.23	17.77	1.915038	1.249687
15	12.0	3.46	1.079181	84.04	15.96	1.924524	1.203032

Table 15. *In Vitro* release data of Diltiazem from F8

S. No	Time (Hrs.)	Square Root of time	Log time	% Drug release	% Drug remained	Log Percentage drug release	Log Percentage drug remain
1	0.0	0	0	0	0	0	0
2	0.5	0.70	-0.30103	9.59	90.41	0.981985	1.956216
3	1.0	1.00	0	27.06	72.94	1.432454	1.862965
4	1.5	1.22	0.17609	39.74	60.26	1.599285	1.780029
5	2.0	1.41	0.30103	52.07	47.93	1.716670	1.680607
6	3.0	1.73	0.47712	68.86	31.14	1.838023	1.493318
7	4.0	2.00	0.60206	75.37	24.63	1.877249	1.391464
8	5.0	2.23	0.69897	78.53	21.47	1.895041	1.331832
9	6.0	2.44	0.77815	82.57	17.43	1.916844	1.241297
10	7.0	2.64	0.84509	85.96	14.04	1.934327	1.147367
11	8.0	2.82	0.90309	87.61	12.39	1.942557	1.093071
12	9.0	3.00	0.95424	88.57	11.43	1.947287	1.058046
13	10.0	3.16	1				
14	11.0	3.31	1.041393				
15	12.0	3.46	1.079181				

Table 16. *In Vitro* release data of Diltiazem from F9

S. No	Time (Hrs.)	Square Root of time	Log time	% Drug release	% Drug remained	Log Percentage drug release	Log Percentage drug remain
1	0.0	0	0	0	0	0	0
2	0.5	0.70	-0.30103	7.75	92.25	0.8893	1.964966
3	1.0	1.00	0	14.20	85.80	1.15228	1.933487
4	1.5	1.22	0.17609	24.86	75.14	1.3955	1.875871
5	2.0	1.41	0.30103	33.53	66.47	1.525453	1.822625
6	3.0	1.73	0.47712	43.62	56.38	1.63968	1.751125
7	4.0	2.00	0.60206	52.85	47.15	1.72044	1.673481
8	5.0	2.23	0.69897	68.64	31.36	1.83657	1.496376
9	6.0	2.44	0.77815	77.63	22.37	1.890029	1.349665
10	7.0	2.64	0.84509	81.50	18.50	1.911157	1.267171
11	8.0	2.82	0.90309	84.38	15.62	1.92623	1.193681
12	9.0	3.00	0.95424	85.75	14.25	1.93323	1.153814
13	10.0	3.16	1				
14	11.0	3.31	1.041393				
15	12.0	3.46	1.079181				

Table 17. FT-IR Spectral data of pure Diltiazem hydrochloride and formulation Containing Diltiazem hydrochloride

Group Frequency of Pure drug(in cm-1)	Frequency of pure drug(in cm-1)	Frequency of F7 (in cm-1)
Aliphatic N-H stretch	3446.91	3421.83
O-CH3,C-H stretch	2966.62	2935.76
Two C=O groups	1743.71, 1681.96	1743.71, 1678.13
N-H df	1255.70	1253.77
Aliphatic C-N stretch	1219.05	1219.05
O-substituted aromatic C-H out of plane deformation	839.06	837.13
p-substituted aromatic C-H out of plane deformation	781.57	782.2

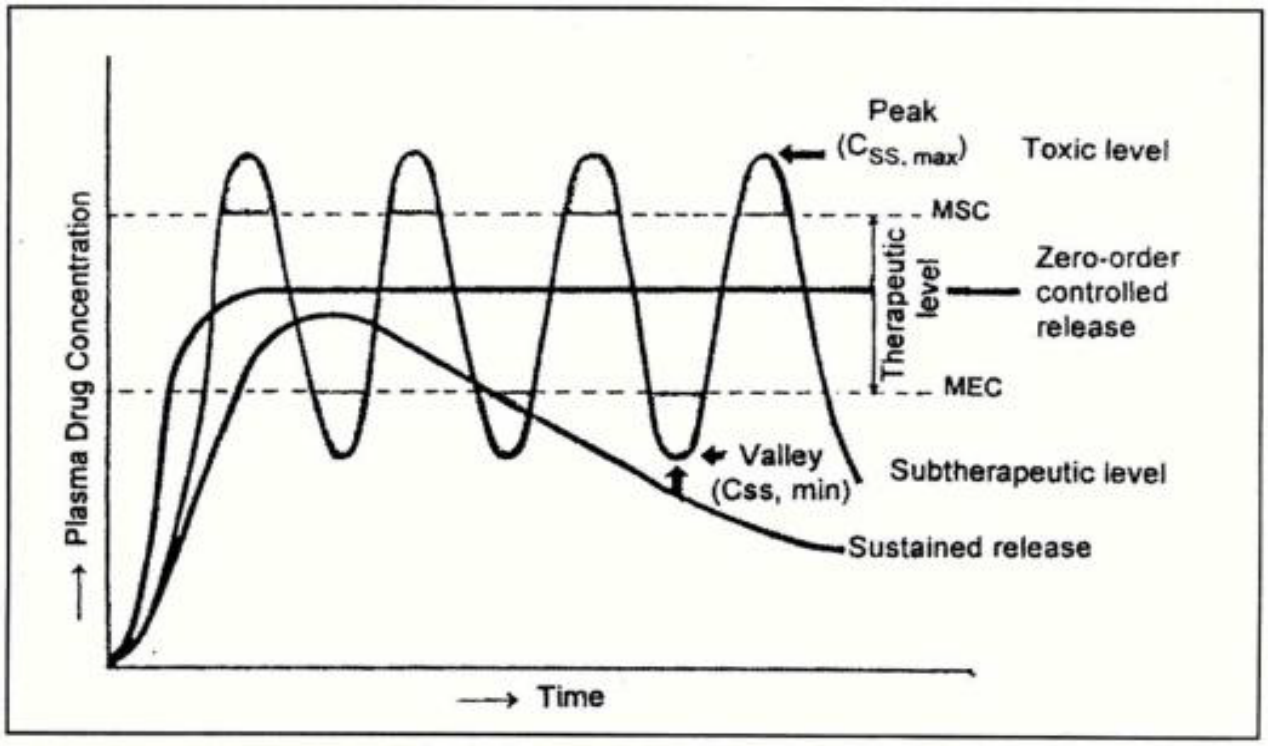

Figure.1. Plasma level profiles following conventional and controlled release dosing

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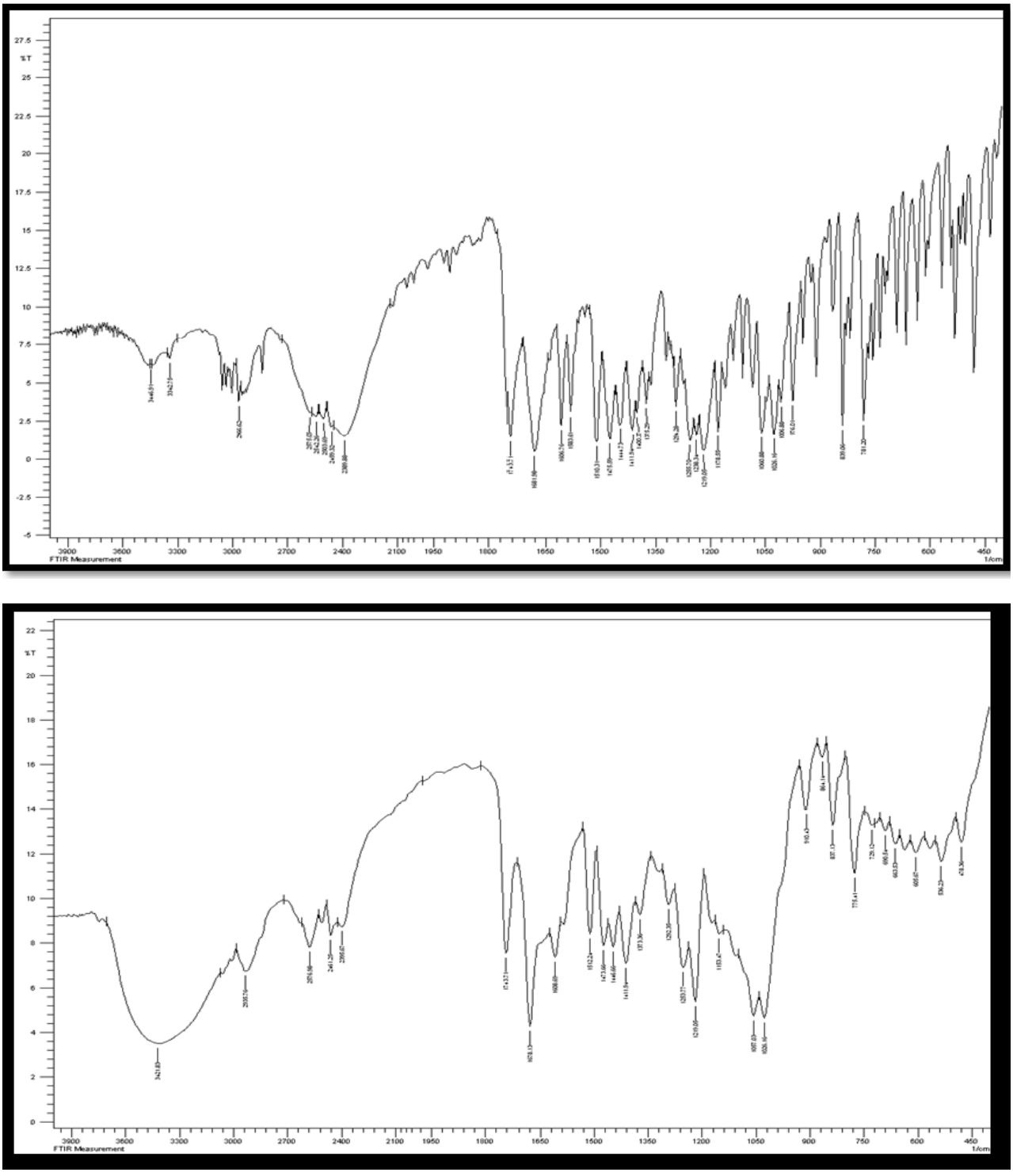

Figure.2. FT-IR spectra of Diltiazem Hydrochloride pure drug, formulation F7

 ISSN-2321-547X

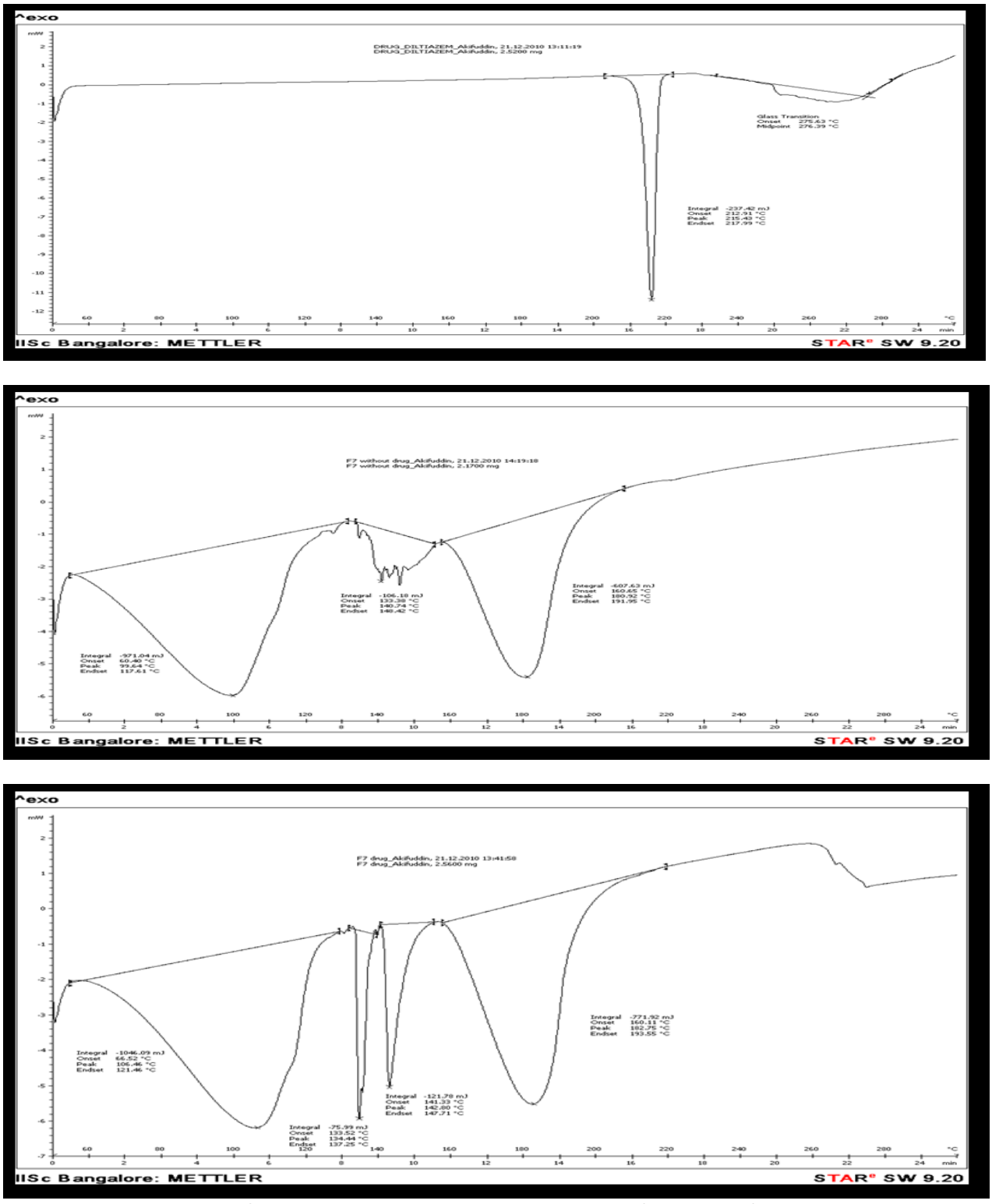

Figure.3. DSC of Diltiazem Hydrochloride pure drug, Drug free beads, formulation F7

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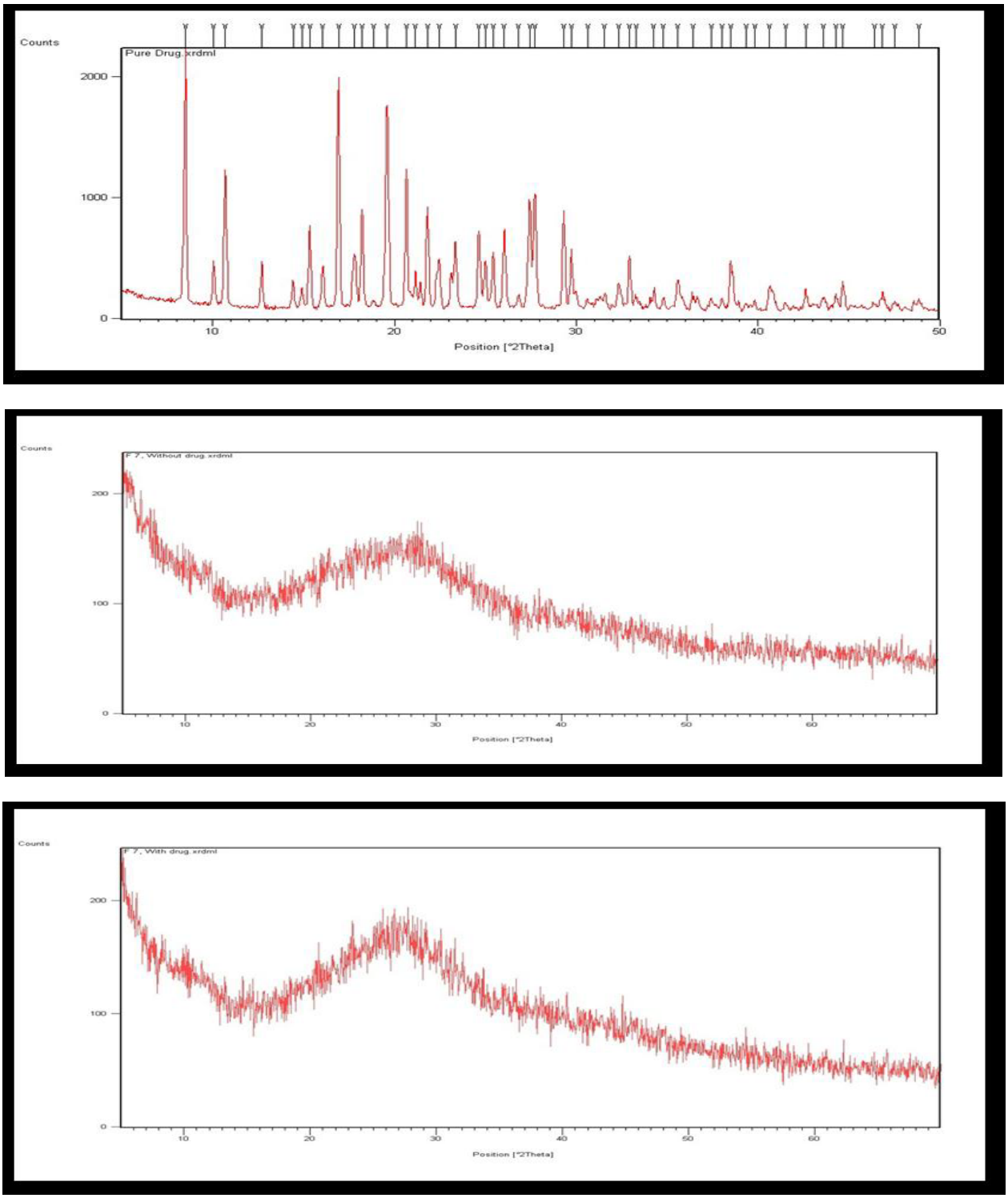

Figure.4. XRD of Diltiazem Hydrochloride pure drug, formulation F7 and Drug free beads

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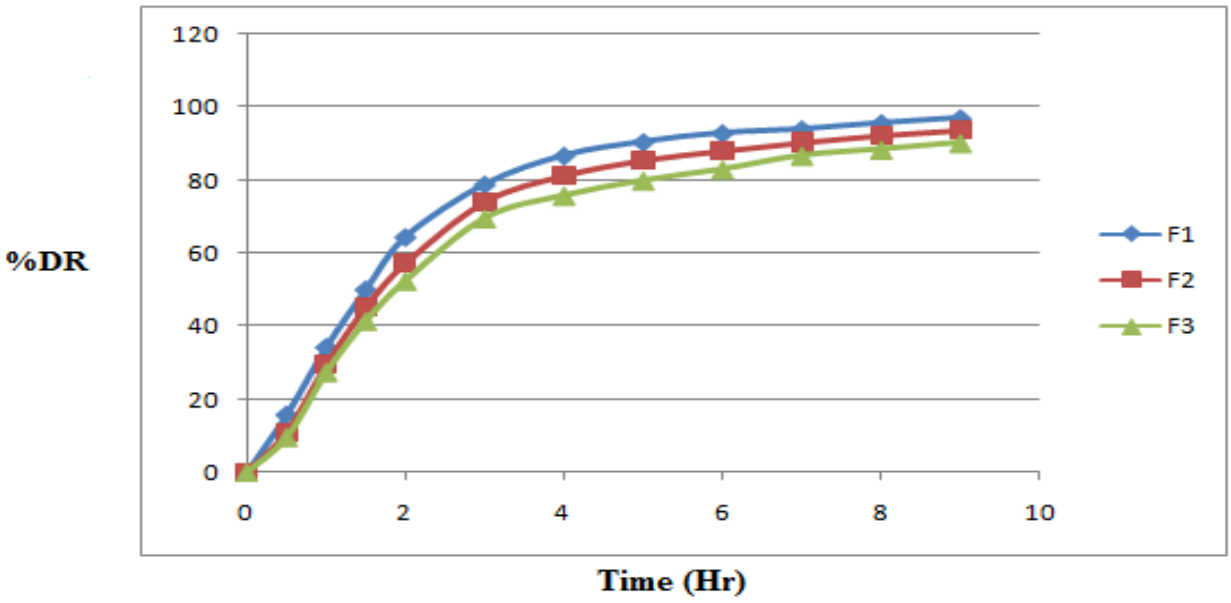

Figure.5. *In vitro* release profile of diltiazem from xanthan gum and CMC beads F1, F2, F3

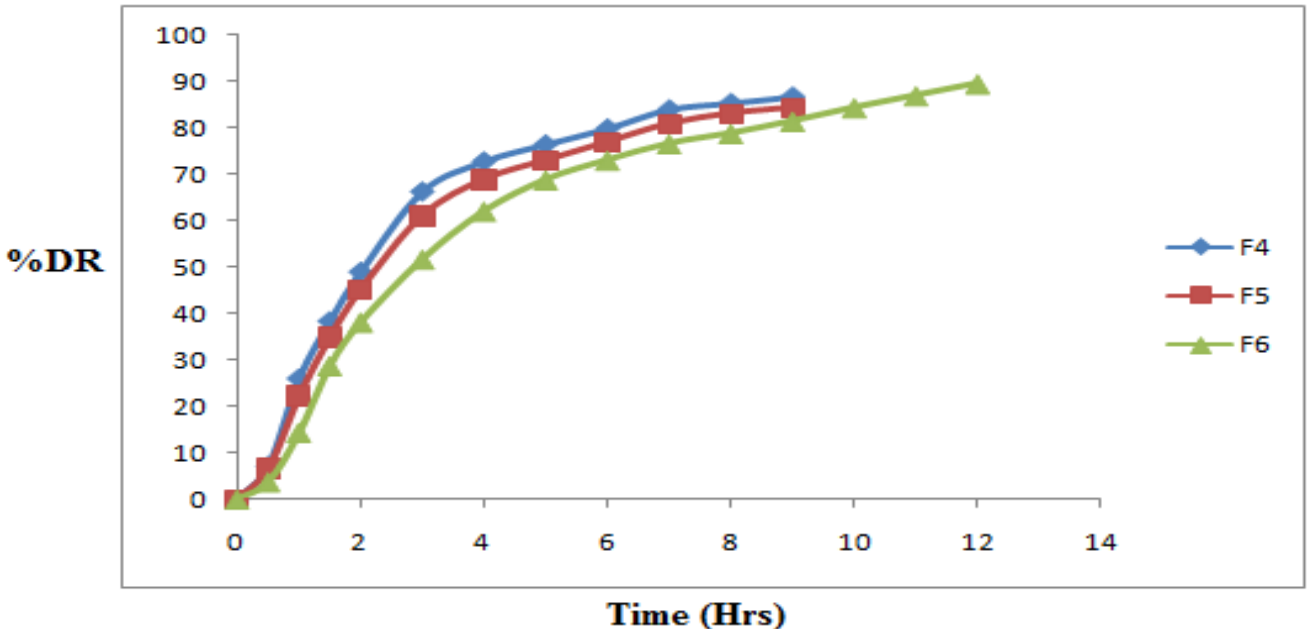

Figure.6. *In vitro* release profile of diltiazem from xanthan gum and CMC beads F4, F5, F6

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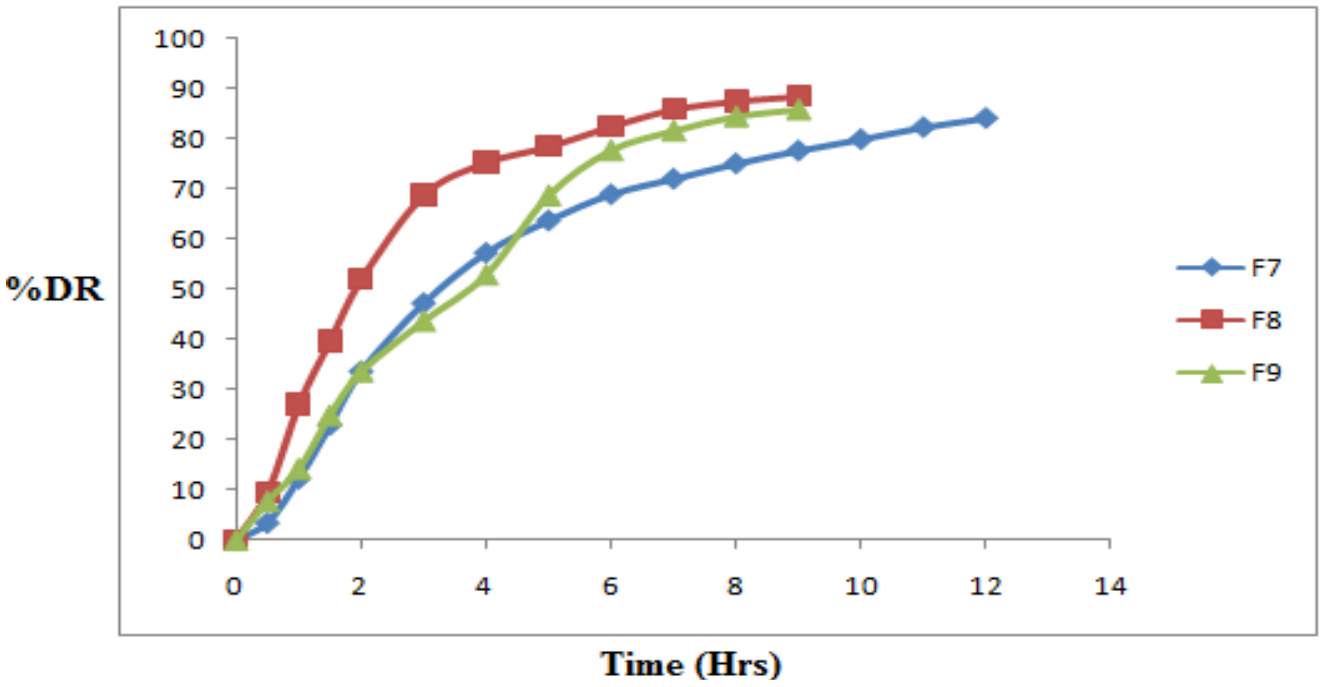

Figure.7. *In vitro* release profile of diltiazem from xanthan gum and CMC beads F7, F8, F9