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PREFORMULATION STUDIES OF DILTIAZEM HYDROCHLORIDE FROM TABLETED MICROSPHERES

Manish Kumar Gupta[1*], Surendra Kumar Swarnkar[2]

[1] Professor and Principal, Jaipur College of Pharmacy, Jaipur, Rajasthan, India
[2] Assistant Professor, LBS College of Pharmacy, Jaipur, Rajasthan, India

ABSTRACT

Microspheres are solid, spherical particles of protein or polymer-based matrix which comprised of a fairly homogeneous mixture of polymer and active agents.It undergoes considerable presystemic metabolism (45-55%) which results in reduced bioavailability. Diltiazem hydrochloride was scanned in the Methanol, acid buffer, pH 1.2and phosphate buffer, pH 7.2. 10 mg of drug was dissolved in methanol in 100 ml in volumetric flask, and volume was made to 100 ml with same solvent. This stock solution was further diluted to get concentration of 10mcg/ml. This solution was scanned in UV-spectrophotometer and characteristic peak was observed at 239 nm for methanol, 237 nm for acid buffer, pH 1.2 and phosphate buffer, pH 7.2. Standard curve of Diltiazem hydrochloride was plotted in Methanol, acid buffer (pH 1.2) and phosphate buffer (pH 7.2). The critical values for regression coefficient in each plot were less than 0.001 (i.e., $P < 0.001$). That indicates that there was a high linear correlationbetween concentration of drug with absorbance.

Keywords: Diltiazem hydrochloride, regression coefficient, bioavailability, Microspheres.

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***Address for Correspondence**

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INTRODUCTION

Oral delivery of drugs is by far the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in formulation, etc. [1] The frequency of administration or the dosing interval of any drug depends upon its half-life or mean residence time (MRT) and its therapeutic index. In most cases, the dosing interval is much shorter than the half-life of the drug resulting in a number of limitations. These limitations can overcome by formulating into Modified-Release dosage forms. Modified-release products provide either delayed-release or extended-release of the drug.[2]

There are three types of controlled drug delivery systems available: [3]

- ***Passive preprogrammed***, in which the release rate is predetermined and is irresponsive to the external biological environment.
- ***Active preprogrammed,*** whose release rate can be altered by a source external to the body (include most metered insulin pumps).
- ***Active, self – programmed,*** modulate release rate of the drug in response to information, registered by a sensor, on the changing biological environment, such as blood sugar level in diabetes.

Biological factors influencing design and performance of sustained / controlled release products [3]

- Absorption
- Distribution

- Metabolism
- Duration of Action
- Side effects
- Margin of safety
- Role of disease state
- Role of circadian rhythm

Microspheres

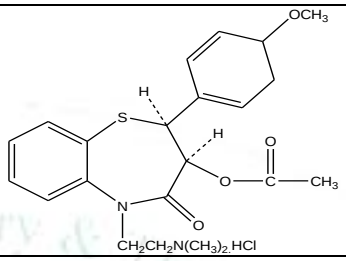
Microspheres are solid, spherical particles of protein or polymer based matrix which comprised of a fairly homogeneous mixture of polymer and active agents. Microspheres usually have diffusion controlled release profiles with a permanent release rate that is controlled kinetically by the particle size, whereas microcapsules usually have diffusion or dissolution controlled release profiles or both. Microcapsules expel their content by a single high burst as the shell breaks or slow releases. [4, 5, 6]

MATERIALS AND METHODS

Drug profile: Diltiazem Hydrochloride

Diltiazem hydrochloride is a calcium channel blocker (benzothiazepine), widely used for the treatment of angina pectoris, arrhythmias and hypertension.

Table 1: Parameter of Drug profile

Description	Properties	Given Data
Chemistry[7, 8]	Chemical Structure	
	Chemical Name	(+)-cis-2,3,4,5-tetrahydro-5-(2-dimethylaminoethyl)-2- (4-methoxyphenyl)-4-oxobenzo[b]thiazepin-3-yl acetatemonohydrochloride
	Molecular Formula	$C_{22}H_{26}N_2O_4S$ .HCl
	Molecular Weight	450.98
	Description	White, crystalline powder or small crystals,Odorless and has a bitter taste
	CAS Registry Number	33286-22-5
	Melting Point	210º C [207.5º C – 212º C]
	Optical Rotation	The optical rotation of a 1% (w/v) solution of diltiazemhydrochloride in water at 25º C ($[\alpha_D^{25}]$) is between +100º and +116º
	Polymorphism	No polymorphs of diltiazem hydrochloride have been reported to date
	pH	pH of saturated solution in water = 3.0 pH of 1.0% (w/w) solution in water = 4.2
	pKa	7.7
	Stability[9]	In 1N hydrochloric acid at 25ºC, 59.5% of the sample was degraded in 24 hrs
Pharmacokinetics	Oral absorption	90% (Uniformly absorbed Throughout the GIT
	Presystemic metabolism	45-55%
	Oral bioavailability	38 ± 11%
	Plasma half life Range	2-11 h
	Mean (single dose)	4.5 h (↔ RD, Aged) (does not change with multiple dosing)
	Peak time	4.0 ± 0.4 h
	Peak concentrations	151±46ng/ml(Following a single 120mg oral dose)
	Volume of distribution	3.3 ± 1.2 liter.kg^{-1} (↔ Aged, ↓ RD)
	Plasma protein binding	80-90%
	Clearance	11.8 ± 2.2 (↔ Aged, ↓ RD)
	Metabolism	Metabolized in the liver and at least six metabolites have been identified
	Urinary Excretion	< 4%
	Concentration – effect relationship	The minimum therapeutic plasma concentration appears to be in the range of 50 – 120 ng/ml
	Therapeutic Uses	Stable/ Unstable angina pectoris, MI, Coronary artery spasm, Hypertension, Arrhythmias, Raynaud's phenomenon, Esophageal motility disorders, Migraine, Primary pulmonary hypertension
	Therapeutic dose	30 to 60 mg (three to four times a day). Loading dose = 0.25 – 0.35 mg/kg over 10 min. Maintenance dose = 5 – 15 mg/h
	Mechanism of Action:[10, 11]	Diltiazem is an inhibitor of calcium ion influx and causes a dose-dependent, inhibition of the transmembrane influx of calcium ions into

		into muscle via the 'L' channel. Diltiazem block calcium channels in cardiac cells at clinically used doses.
Pharmacodynamic Parameters		Therapeutic Index – Wide [LD_{50} in male ,female mice, male, female rats : 740, 640, 560, 610 mg/kg orally] Plasma drug concentration response – Good
Physical Property[8,12]	Solubility of Diltiazem-HCl in various solvents	In Chloroform, Methanol and Water: Freely soluble In Dehydrated alcohol: Sparingly soluble In Benzene: Practically insoluble. In Ether: Insoluble
	Solubility of Diltiazem-HCl at Various pH Buffer[13](mg/ml) ± %RSD	HCl (1.2): 658.83 ± 4.40 Phosphate Buffer (5.0)597.51 ± 1.54 Phosphate Buffer (7.4)593.20 ± 3.67 Phosphate Buffer (8.0)511.06 ± 3.94
Category		Calcium channel blocker, Antianginal, Antihypertensive

Therapeutically Beneficial Parameters [10]

The area under the plasma concentration curve (AUC) is substantially higher in chronic dosing, than after a single dose. Therefore, following a 90mg single dose, the area was 505 µg liter^{-1}.h^{-1}, but when the same dose was given every 6 hour for 4 days, the AUC increased to 1216 µg liter^{-1}.h^{-1}

- Diltiazem hydrochloride is approved for clinical use in the United States.
- It is not available in combination preparations.

Preformulation Studies

Scanning of the drug (Diltiazem hydrochloride)

Diltiazem hydrochloride was scanned in the following solvent and buffers –

i) Methanol

ii) Acid Buffer, pH 1.2

iii) Phosphate Buffer, pH 7.2

i) Scanning of the drug in solvent methanol

10 mg of drug was dissolved in methanol in 100 ml in volumetric flask, and volume was made to 100 ml with same solvent. This stock solution was further diluted to get concentration of 10 mcg/ml. This solution was scanned in UV-spectrophotometer and characteristic peak was observed at 239 nm.

ii) Scanning of the drug in acid buffer, pH 1.2

10 mg of drug was dissolved in acid buffer pH, 1.2 in a 100 ml volumetric flask, and volume was made to 100 ml with same solvent. This stock solution was further diluted by acid buffer to get concentration of 10 mcg/ml. This final solution was scanned in UV-spectrophotometer. The characteristic peak was observed at 237 nm.

iii) Scanning of drug in phosphate buffer, pH 7.2

10 mg of drug was dissolved in phosphate buffer pH, 7.2 in a 100 ml volumetric flask, and volume was made to 100 ml with same solvent. This stock solution was further diluted by phosphate buffer to get concentration of 10mcg/ml. This final solution was scanned in UV-spectrophotometer. The characteristic peak was observed at 237 nm.

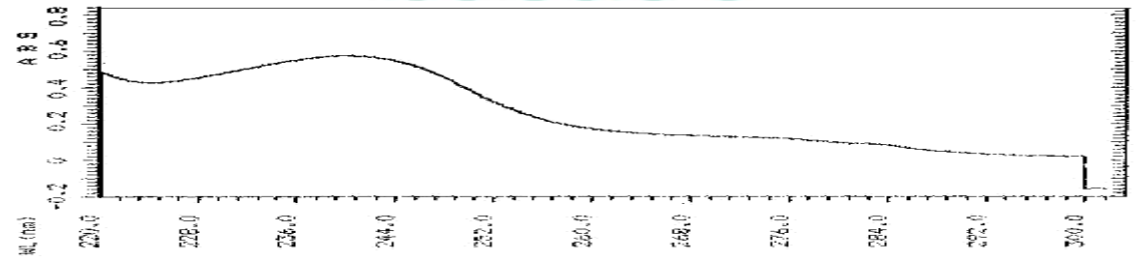


Figure 1: UV Spectrum of Diltiazem hydrochloride in solvent methanol)

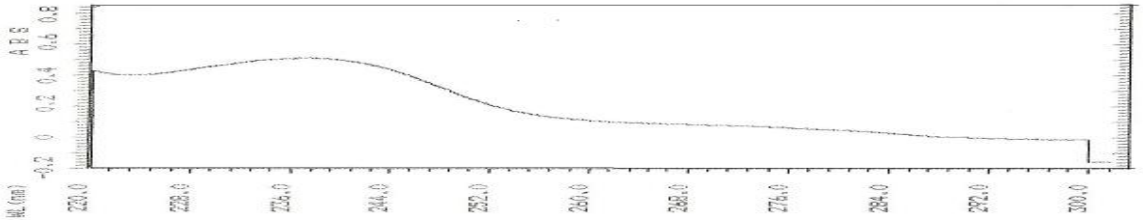


Figure 2: UV Spectrum of Diltiazem hydrochloride in acid buffer pH 1.2)

Table 2: Summary of the scanning of Diltiazem hydrochloride in solvent methanol and buffers

S. No.	Amount of Diltiazem Hydrochloride (mg)	Solvent used to make up volume	Final volume (ml)	Concentration of stock solution (mcg/ml)	Concentration of scanning solution (mcg/ml)	Scanning range	Characteristic peak, λ_{max} (nm)
1	10	Methanol	100	100	10	220 nm – 300 nm	239
2	10	Acid Buffer, pH 1.2		100	10		237
3	10	Phosphate Buffer, pH 7.2		100	10		237

RESULTS

Infrared Spectroscopy

The IR spectrum of pure drug, Eudragit RL100, Eudragit RS100, Eudragit RLPO, Eudragit RSPO, Magnesium stearate, were recorded in potassium bromide using Shimadzu FTIR – 8400 S(CE). The range of scanning was 500 cm^{-1} – 4000 cm^{-1}.

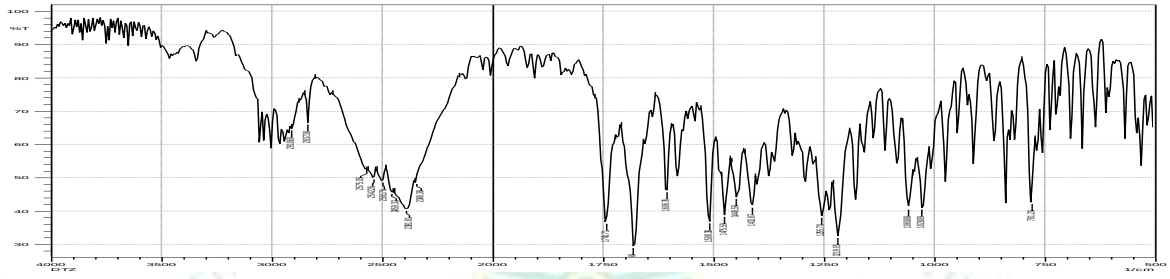


Figure 3: IR Spectrum of Diltiazemhydroccloride

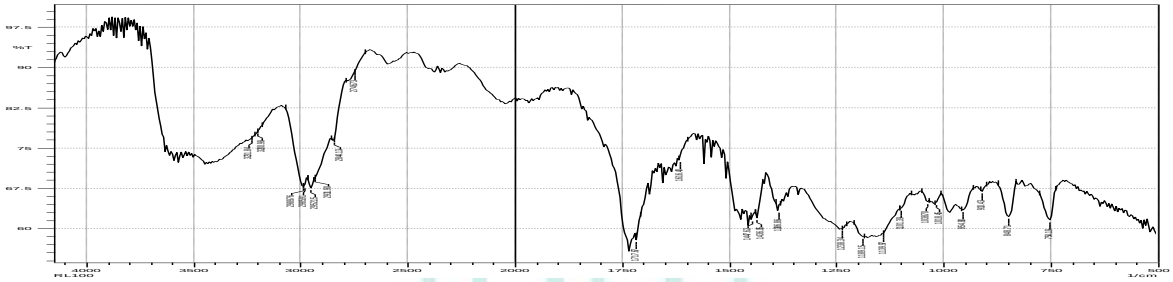


Figure 4: IR Spectrum of Eudragit RL100

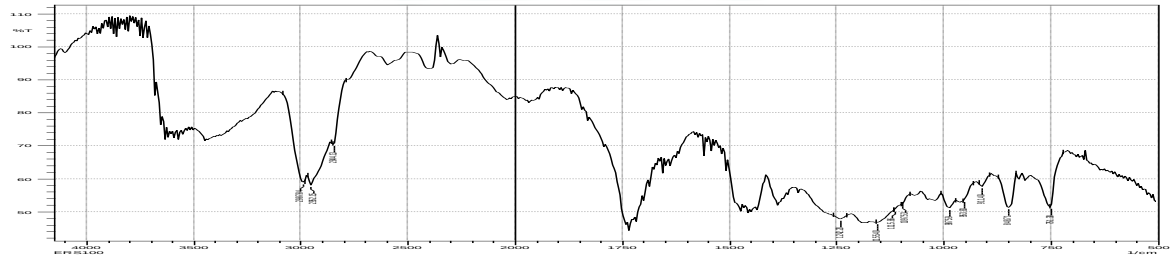


Figure 5: IR Spectrum of Eudragit RS100

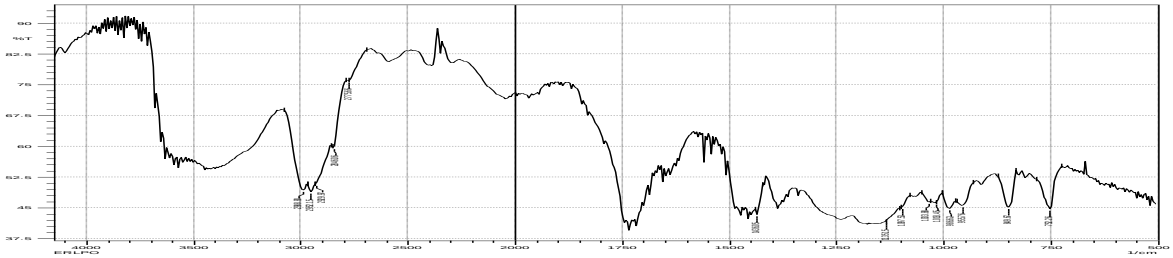


Figure 6: IR Spectrum of Eudragit RLPO

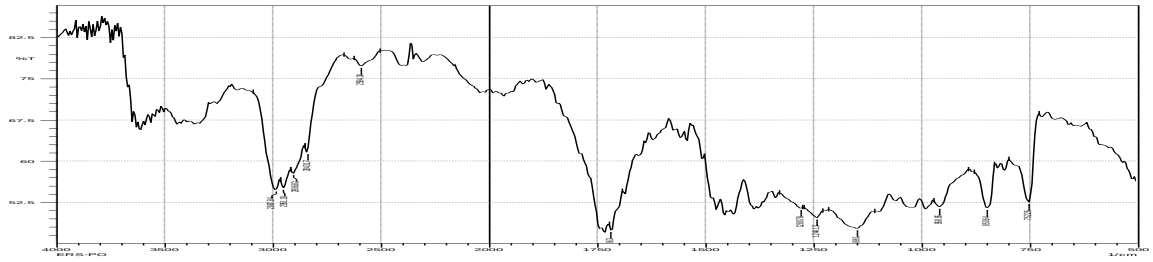


Figure 7: IR Spectrum of Eudragit RSPO

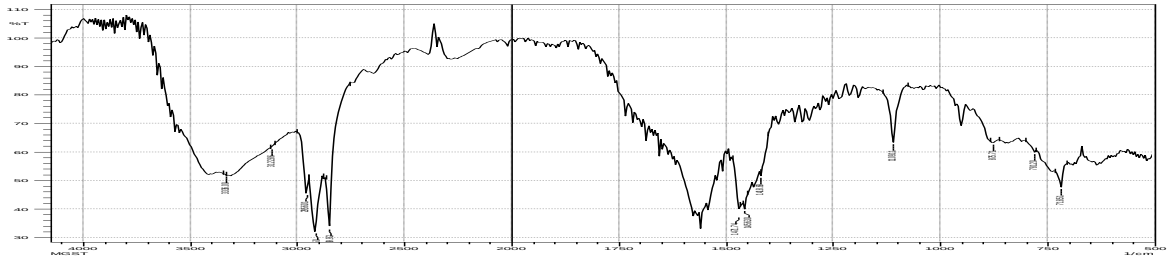


Figure 8: IR Spectrum of Magnesium Stearate

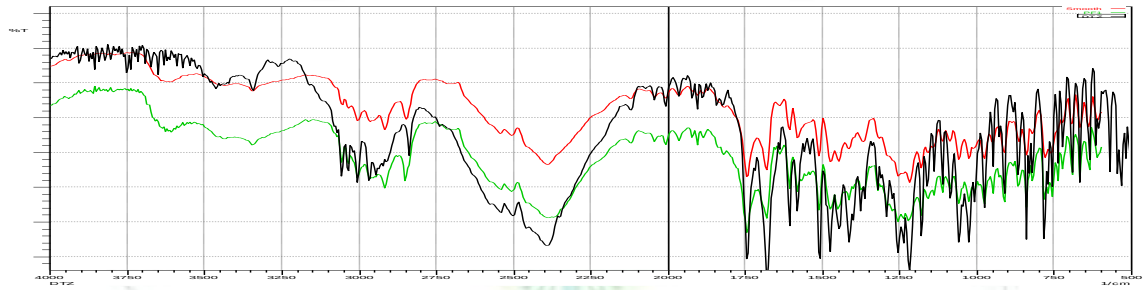


Figure 9: IR spectrum of DTZ.HCl, F1, PF1 (Physical mixture corresponding to F1)

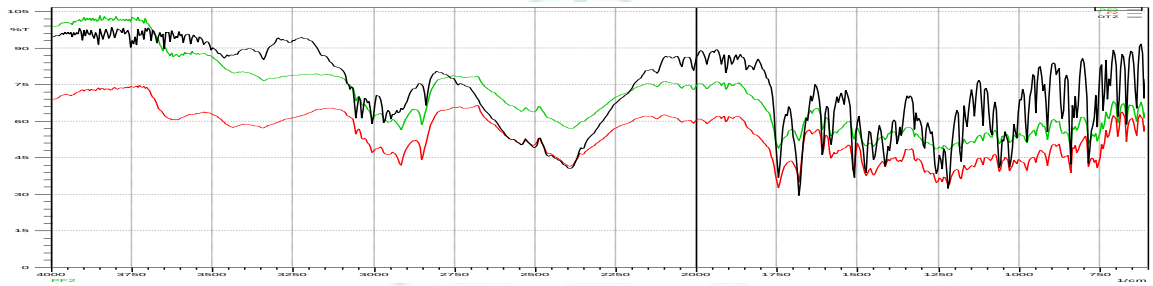


Figure 10: IR spectrum of DTZ.HCl, F2, PF2(Physical mixture corresponding to F2)

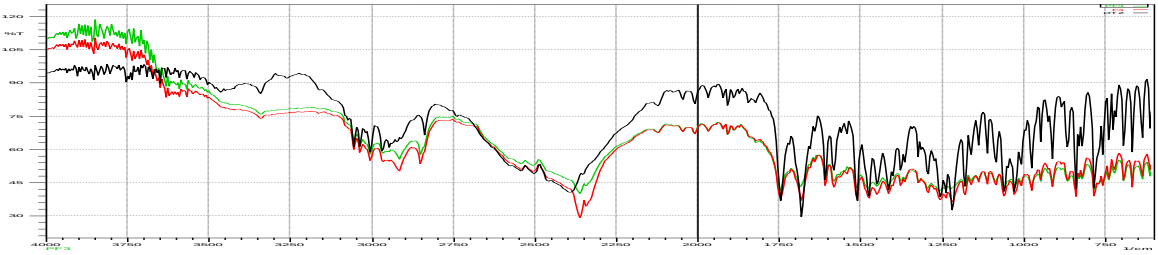


Figure 11: IR spectrum of DTZ.HCl, F3, PF3(Physical mixture corresponding to F3)

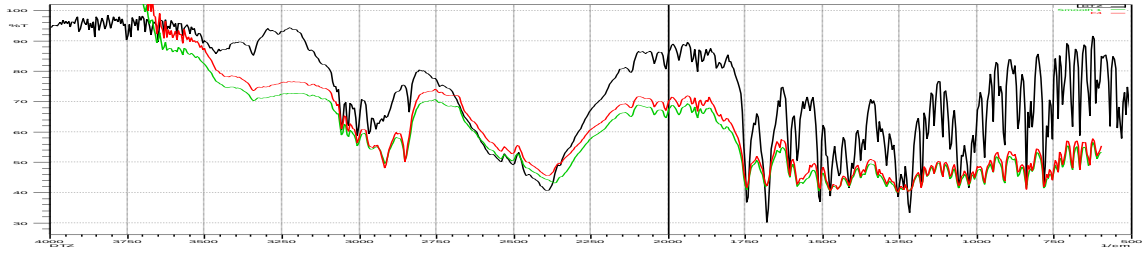


Figure 12: IR spectrum of DTZ.HCl, F4, PF4(Physical mixture corresponding to F4)

Microspheres have received considerable attention in pharmaceutical and biomedical application, specifically achieving sustained release and controlled release objectives. Thus, it is an useful method for prolonging drug release from dosage forms, reducing adverse effects and to deliver drugs in a controlled manner. According to Biopharmaceutical Classification System (BCS), Diltiazem hydrochloride is having the characteristics of high solubility, high permeability. Thus it is covered under BCS class – I category. So, Diltiazem hydrochloride is a suitable candidate for sustain release formulation.

Scanning and Standard plots of Diltiazem hydrochloride

Scanning of Diltiazem hydrochloride was performed into Methanol, acid buffer (pH 1.2) and phosphate buffer (pH 7.2). The characteristic peak, λ_{max} was found to be at 237, 237 and 239 nm respectively.

Standard curve of Diltiazem hydrochloride was plotted in Methanol, acid buffer (pH 1.2) and phosphate buffer (pH 7.2). The critical values for regression co-efficient in each plot were less than 0.001 (i.e., $P < 0.001$). That indicates that there was high linear correlation between concentrations of drug with absorbance.

IR Spectroscopy (FTIR)

This technique is used to determine any chemical interactions between drug and excipients. The Fourier transformed infrared (FTIR) spectra of drug, polymers, formulations and mixtures were obtained using FTIR Spectrophotometer (FTIR – 8400S (CE), SHIMADZU). The intermediate mixtures of drug with each polymer were prepared for each formulation of F_1, F_2, F_3 and F_4 as microspheres and subjected to analysis by FTIR. Spectra is shown in Fig and results were tabulated below-

Table 3: Wave- number of different functional groups present in Diltiazem.HCl

Code	Composition	Peak for Diltiazem hydrochloride				
		Aromatic C-H Stretch (cm^{-1})	O-CH_3 C-H stretch (cm^{-1})	Amine HCl N-H stretch (cm^{-1})	Acetate C=O stretch (cm^{-1})	Lactam C=O stretch (cm^{-1})
DTZ.HCl	Diltiazem Hydrochloride	3057.27	2837.38	2391.81	1743.71	1681.98
F1 PF1	Formulation F1 DTZ: ERL 100	3055.35 3057.27	2847.03 2839.31	2391.81 2389.88	1743.71 1745.64	1681.98 1681.98
F2 PF2	Formulation F2 DTZ: ERS100	3055.35 3057.27	2850.88 285088	2389.88 2389.88	1743.71 1745.64	1681.98 1681.98
F3 PF3	Formulation F3 DTZ: ERL PO	3057.27 3057.27	2850.88 2839.31	2360.95 2362.88	1745.64 1745.64	1681.98 1685.84
F4 Pf4	Formulation F4 DTZ: ERS PO	3057.27 3055.35	2850.88 2850.88	2387.95 2366.74	1745.64 1745.64	1681.98 1683.91

Diltiazem hydrochloride is having O-CH_3, Amine, Acetate, Lactam as functional groups. These are the main sites where the chemical interaction may occur. After observing the spectra and above data, it could be concluded that the peak of these functional groups are intact in the intermediate mixtures and final formulations (Microspheres). As there was no shifting, deleting and broadening of the peak observed in the spectrum, it can be concluded that no chemical interactions had been occurred.

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