Research Article

Formulation and Evaluation of Microspheres of Diltiazem Hydrochloride by Spray Drying Technique

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ABSTRACT

Microencapsulation technology is an innovator in the encapsulation science. This technology forms a basis for the development of various micro and nano drug loaded capsules. Spray drying is defined as the transformation of a feed from a fluid state (solution, dispersion, or paste) into a dried particulate form by spraying the feed into a hot gaseous dry in medium. In the present study Diltiazem Hydrochloride was used as drug and there was usage of some natural and synthetic polymers were used like Guargum, Xanthan gum, Eudragit L100, Eudragit S100, HPMC K4M. The optimized batch was of polymer Eudragit L100which is a synthetic polymer which shows controlled release tendency for any drug delivery system. In this formulation batch F6 having Eudragit L100as polymer in the concentration of 1:2 ratio by using isopropyl alcohol as solvent gives maximum drug release for 12hrs. as 100.44 % and gives controlled release for 12 hrs. which is better than other batches. Where other polymers like HPMC K4 M, Guargum, Xanthan gum and Eudragit S100was unable to give controlled release. All the prepared formulations show drug content uniformity in the range of 60-70%, the optimized batch show drug content uniformity 70% and follows zero order kinetics.

Keywords: Spray drying, Micro-encapsulation, Diltiazem Hydrochloride, Eudragit L100.

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INTRODUCTION

Controlled drug delivery systems are designed to release drug in a controlled manner over time. Usually, the aim is to release the drug over long periods at a constant (zero-order) rate, confined to the drug's therapeutic window, although in some therapies a constant release is not desirable. In diffusion-controlled delivery systems, the diffusion of drugs through the polymer matrix and/or porous channels limits the release rate. This type of delivery system may be a matrix system where the drug is distributed in a polymer phase, or reservoir system in which a polymer surrounds a drug core[1]. Mathematical modeling of diffusion-controlled systems depends on the type of delivery system (reservoir or matrix), the pore size of the polymer phase (nonporous, microporous, or macroporous), the drug solubility in the delivery system (dissolved or dispersed), and the geometric characteristics of the delivery system.[1]

Microencapsulation[1]

Microencapsulation is a process by which very tiny droplets or particles of liquid, solid or even gas materials are surrounded or coated with a continuous film of polymeric material. It includes Bio-encapsulation which is more restricted to the entrapment of a biologically active substance (from DNA to entire cell or group of cells for example) generally to improve its performance or enhance its shelf life. The definition has been expanded, and includes more foods. Every class of food ingredient has been encapsulated; flavors are the most common.

The technique of microencapsulation depends on the physical and chemical properties of the material to be encapsulated. These micro-capsules have a number of benefits such as Converting liquids to solids, separating reactive compounds, providing environmental protection, improved material handling properties. Active materials are then encapsulated in micron-sized capsules of barrier polymers.

Reason for Micro- encapsulation[2-7]

There are many reasons towards microencapsulation. In some cases, the core must be isolated from its surroundings, as in isolating vitamins from the deteriorating effects of oxygen, retarding evaporation of a volatile core, improving the handling properties of a sticky material or isolating a reactive core from chemical attack. There are several reasons why substances may be encapsulated

1. To control release of the active components for delayed (timed) release or long-acting (sustained) release.
2. The drugs, which are sensitive to oxygen, moisture or light, can be stabilized by microencapsulation.
3. Incompatibility among the drugs can be prevented by microencapsulation.

4. Many drugs have been microencapsulated to reduce toxicity and GI irritation including ferrous sulphate and KCl.
5. Alteration in site of absorption can also be achieved by microencapsulation.
6. Toxic chemicals such as insecticides may be microencapsulated to reduce the possibility of sensitization of factorial person.
7. Bakan and Anderson reported that microencapsulated vitamin A palmitate had enhanced stability.
8. A liquid can be converted to a pseudo-solid for easy handling and storage.
9. Retarding evaporation of a volatile core, improving the handling properties of a sticky material, or isolating a reactive core from chemical attack.

Micro- encapsulation Techniques.

Various techniques are available for the encapsulation of core materials. Broadly the methods are divided into three types. Different types of micro-encapsulation techniques are-[8-15]

1. Chemical methods,
2. Physico-chemical methods, and
3. Physico-mechanical methods.

There numerous technologies have been available for the encapsulation of core material have been reported. These different microencapsulation techniques are more relevant to the coating industries and also provide a comprehensive review of recently developed methods. In general, microencapsulation techniques are divided into two basic groups, namely chemical and physical, with the latter being further subdivided into physico-chemical and physico-mechanical technique.

Table 1: Techniques of formulation of microencapsule

Sr. No	Techniques	Methods used	Particle size range [µm]
1	Coacervation	Physico–Chemical	2–1200
2	Polymer-polymeric compatibility	Physico–Chemical	0.5–1000
3	Encapsulation by supercritical Fluid Encapsulation by Polyelectrolyte multilayer	Physico-Chemical	0.02–20
4	Phase Inversion	Physico–Chemical	0.5—5.0
5	Hot Melt	Physico–Chemical	1—1000
6	Spray-drying	Physico–Mechanical	5–5000
7	Fluidized-bed technology	Physico–Mechanical	20–1500
8	Pan coating	Physico–Mechanical	600–5000
9	Spinning disc	Physico–Mechanical	5–1500
10	Co-extrusion	Physico–Mechanical	250–2500
11	Interfacial polymerization	Physico–Mechanical	0.5–1000
12	In situ polymerization (0.5–1100 um)	Physico–Mechanical	0.5–1100
13	Layer-by-layer (LBL) assembly	Physico-Chemical	0.02–20
14	Sol-gel encapsulation	Physico-Chemical	2–20

Spraydrying[17]

Microencapsulation by spray-drying is a low-cost commercial process which is mostly used for the encapsulation of fragrances, oils and flavors. Spray drying is the continuous transformation of feed from a fluid state into dried particulate form by spraying the feed into a hot drying medium. An emulsion is prepared by dispersing the core material, usually an oil or active ingredient immiscible with water; into a concentrated solution of wall material until the desired size of oil droplets are attained. The resultant emulsion is atomized into a spray of droplets by pumping the slurry through a rotating disc into the heated compartment of a spray drier.[18] There the water portion of the emulsion is evaporated, yielding dried capsules of variable shape containing scattered drops of core material. The capsules are collected through continuous discharge from the spray drying chamber. This method can also be used to dry small micro-encapsulated materials from aqueous slurry that are produced by chemical methods. Lycopene has been microencapsulated inside gelatin microcapsules by using this technique.

Principles of the Spray Drying Process:

Spray drying is defined as the transformation of a feed from a fluid state (solution, dispersion, or paste) into a dried particulate form by spraying the feed into a hot gaseous dry in medium. It is a continuous one-step processing operation in which four different phases can be distinguished, namely:

1. Atomization of the feed,
2. Mixing of spray and air,
3. Solvent evaporation and
4. Product separation.

The size of microspheres can be controlled by the rate of spraying, the feed rate of polymer drug solution, nozzle size, and the drying temperature. This method of microencapsulation is particularly less dependent on the solubility characteristics of the drug and polymer and is simple, reproducible, and easy to scale up.[19]

Spray drying serves as a microencapsulation technique when an active material is dissolved or suspended in a melt or polymer solution and becomes trapped in the dried particle. The main advantages is the ability to handle labile materials because of the short contact time in the dryer, in addition, the operation is economical. In modern spray dryers the viscosity of the solutions to be sprayed can be as high as 300mPa.

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Spray drying and spray congealing processes are similar in that both involve dispersing the core material in a liquefied coating substance and spraying or introducing the core - coating mixture into some environmental condition, whereby, relatively rapid solidification (and formation) of the coating is affected.

The principal difference between the two methods, is the means by which coating solidification is accomplished. Coating solidification in the case of spray drying is effected by rapid evaporation of a solvent in which the coating material is dissolved. Coating solidification in spray congealing methods, however, is accomplished by thermally congealing a molten coating material or by solidifying a dissolved coating by introducing the coating - core material mixture into a non-solvent. Removal of the non-solvent or solvent from the coated product is then accomplished by sorption, extraction, or evaporation techniques.[20-23.]

MATERIALS AND METHODS

Materials

Drug- Diltiazem Hydrochloride.

Polymers and Excipients- HPMCK4M, Eudragit S 100, Eudragit L 100, Gaur Gum.

Method

Preparation of Spray dried Microspheres

Spray dried microspheres of Diltiazem Hydrochloride were prepared by using Hydroxypropyl methylcellulose such as HPMC K4M polymers, Natural polymers such as Xanthan Gum, Gaur Gum and Synthetic polymers such as Eudragit L100 and Eudragit S100 were used in different ratio by using Isopropyl alcohol and ethanol as solvent for preparation of Spray dried microspheres of Diltiazem Hydrochloride. Thus in the present study, the firstly different batches of microspheres were prepared by taking the drug and polymer in combination in ratio as Drug: Xanthan Gum, Drug: Guar Gum, Drug: in 1:1 ratios. Then these are used in combination as 1:1 and 1:2 ratio with viscosity grades of HPMC, i.e. K4M, Eudragit S100, Edragit L100 by using Hydro alcoholic solvent system which contains mixture of water and Isopropyl alcohol in 40: 60 ratio respectively.

Procedure

The spray dried microspheres were prepared using a SPD-E-111 spray dryer. Firstly, Eudragit S100was dissolved in Isopropyl alcohol and it was uniformly mixed by using magnetic stirrer. Then drug was dissolved in distilled water and it was uniformly mixed by using magnetic stirrer.

This solution was spray dried with the process parameters as follows.

1. Inlet Temperature- 80°C
2. Inlet Temperature High - 90°C
3. Outlet Temperature - 45°C
4. Outlet Temperature High - 60°C
5. Feed Rate - 1ml/min
6. Atomizing Air Pressure - 1kg/m^2
7. Nozzle Diameter - 0.5/0.7/1.0mm
8. Aspiration Flow - 50 Nm^3/hr

Table 2: Formulation Batches of Diltiazem Hydrochloride Spray dried microspheres (Quantity in mg)

Name of Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Diltiazem Hydrochloride	30	30	30	30	30	30	30	30
Xanthan Gum	30	---	--	--	--	--	--	--
Gaur Gum	--	30	60	--	--	--	--	--
HPMCK4M	--	--	--	30	--	--	--	--
EudragitL100	--	--	--	--	30	60	--	--
EudragitS100	--	--	--	--	--		30	60
Mannitol	120	120	120	120	120	120	120	120
Aerosil	120	120	120	120	120	120	120	120
Magnesium Stearate	3%	3%	3%	3%	3%	3%	3%	3%
Talc	1%	1%	1%	1%	1%	1%	1%	1%

Evaluation of Batches

1. Determination of λ max:

The standard solutions of Diltiazem Hydrochloride were scanned in the range of 200-400 nm against Distilled water as a blank. Diltiazem Hydrochloride showed maximum absorbance at 237nm.Calibration curve of Diltiazem Hydrochloride in Distilled water

2. Preparation of standard stock solution:

A standard stock solution containing 1000 µg/ml was prepared by dissolving 100 mg of Diltiazem Hydrochloride in 100 ml of Distilled water.

Preparation of the test solution:

Diltiazem hydrochloride:

The standard stock solution containing 1000µg/ml of Diltiazem hydrochloride, was prepared in Distilled water, from this stock solution pipette out and dilutions were prepared as 10,20,30,40,50 µg/ml and absorbance was taken at 237nm.

3. Pre formulation studies:

In the pre formulation studies Bulk density, Tapped density, Compressibility index, Hausner's ratio, Angle of repose, were performed.

4. Particle size determination:

Particle size determination was performed by Scanning Electron microscopy method.

5. Percentage Drug Entrapment Efficacy (%DEE):

The yield of microencapsules were determined by comparing the whole weight of Microencapsules formed against the combined weight of the copolymer and drug.

$$\%\ Practical\ yield = \frac{Mass\ of\ microencapsules\ obtained}{Total\ weight\ of\ drug\ and\ polymer} \times 100$$

6. Drug Content Uniformity:

Accurately weighed micro- encapsules equivalent to 100mg were suspended in100 ml of Distilled water, it was shake for 30 min and kept for 24hrs. Next day it was stirred for 5 min and filtered. After suitable dissolution, the drug content in the filtrate was analyzed spectrophotometrically at using Shimadzu UV spectrophotometer.

The drug content uniformity was calculated by-

$$Percentage\ Drug\ Entrapment\ Efficiency = \frac{Actual\ drug\ content}{Theoretical\ drug\ content} \times 100$$

7. Pre formulation testing:

Preformulations Testing of powder blends all the batches were performed like Bulk Density, Tapped Density, Hausner's ratio, Angele of repose, Compressibility Index.

8. Formulation testing:

In this Hardness, Thickness, Weight variation, Friability, Drug Content Uniformity tests were performed using 10 tablets of each batch shown in Table 8.

9. In-vitro Release Profile Study of Formulated Tablets:

Method: In vitro drug release studies were carried out using USP 25 (Type II) apparatus in 900ml of dissolution medium (n=3) maintained at 37±10^{0}C at a speed of 100 rpm. Distilled water was used as dissolution medium to avoid the effects of pH change on the solubility of Diltiazem Hydrochloride as it decreases with the increasing pH. Aliquots of 10ml were withdrawn at predetermined time intervals using calibrated pipette during a 12 hours period and filtered. An equivalent amount of fresh dissolution medium, maintained at 37±10^{0}C was added after withdrawing each sample to maintain the sink conditions. The drug concentrations in the sample analyzed spectrophotometrically (double beam UV, Thermo) at 237nm. The mean of three readings was used to determine concentration.

10. Drug Kinetic Study:

The release data obtained from various batches were studied with respect to the effect of drug: polymer ratio, diluents ratio. To analyze the mechanism of drug release from the formulation, the dissolution profile of optimized batches was fitted to zero-order, first-order, Higuchi, Hixson-Crowell, Korsemeyer and Peppas to ascertain the kinetic modeling of drug release as shown in

$$Mass\ loss\ (\%) = \frac{OriginalWeight - Remaining\ (Dry)\ Weigh}{OriginalWeight} \times 100$$

11. Morphological Study by using SEM:

Scanning electron microscopy (SEM): The surface topography of (optimized) microspheres were examined by Scanning Electron microscope. The sample was loaded on copper sample holder and sputter coated with platinum. The morphology of optimized batches of tablet was characterized by scanning electron microscopy. Samples were mounted on round brass stubs (12mm diameter) using double-backed adhesive tape and then sputter coated for 8 min at 1.1 LV under argon atmosphere with gold-palladium before examination under the scanning electron microscope (JEOL JSM-6100 Scanning Electron Microscope, Japan). The images were captured on an Ilford PANF 50 black and white 35mm film.

12. FT-IR Spectroscopy:

It's important to check any kind of interaction between drug candidate and polymer. The polymers which are to be incorporated into formulation should be compatible with the drug. This compatibility study or interaction study was done using Fourier transformed infrared spectroscopy. IR spectra of pure Diltiazem Hydrochloride and polymers viz. HPMC K4M were taken separately. Then to know if there is any interaction between drug and polymer, IR spectra of Diltiazem Hydrochloride and other polymers were taken in combination (Figure 4).

RESULTS AND DISCUSSION

Calibration curve of Diltiazem Hydrochloride

Calibration curve of Diltiazem Hydrochloride in Distilled Water 100 ml of drug Diltiazem Hydrochloride was dissolved in Distill water and volume was make up to 100 ml. And dilutions were made as 10,20,30,40, 50 µg/ml and absorbance were taken at 237 nm. It is given in figure 1.

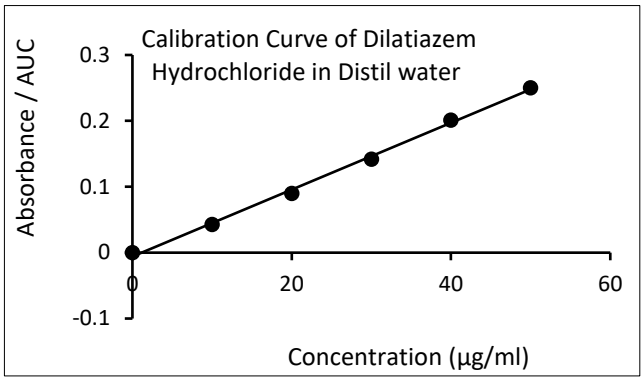

Figure 1: Calibration curve Diltiazem Hydrochloride in Distilled water.

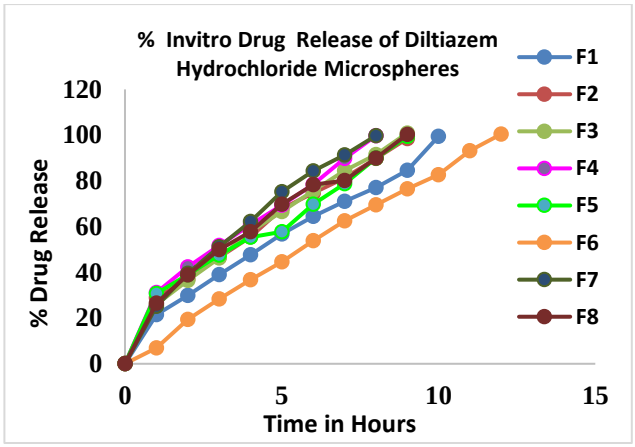

Figure 2: % *In vitro* drug release of Diltiazem Hydrochloride Microspheres.

Table 4: Various Characterization of Diltiazem Hydrochloride Microspheres

Formulation	Drug Entrapment Efficiency	
	% Drug Loading	% Drug Entrapment
F1	3.92	92.72
F2	4.27	97.48
F3	4.99	91.27
F4	4.050	93.47
F5	2.75	94.59
F6	3.725	99.01
F7	5.10	95.45
F8	2.80	98.18

Preformulation Studies:

All the preformulation studies like bulk density, tap density, angle of repose etc, physical characterization of the pre formulation studies like Bulk density, tapped density, %Compressibility, Hausners ratio and angle of repose were performed and these are mentioned in table 3.

Morphological Study by using Scanning Electron Microscopy (SEM)

Morphology of Microspheres was examined by scanning electron microscopy. The smooth surface of such microspheres as seen by SEM might be due to this complete homogeneity of drug, polymer, fillers and shapers. The outer surface of the microspheres was smooth and dense as shown in Figure no 3. The surface topography revealed a spherical surface for all the formulations and a round cavity enclosed by an outer shell composed of the drug and polymer. They appeared to be hollow presumably because of the rapid escape of volatile solvent from the polymer matrix. This hollow nature was also responsible for the microspheres to enhance the surface area for solubility.

Table 3: Preformulation Testing of Diltiazem HCL Microspheres (n = 3)

Sr.No.	Formulation Code	Bulk density (gm/cm^3)	Tapped density (g/cm^3)	Compressibility Index (%)	Hausner's Ratio	Angle of Repose (θ)
1	F1	0.51±0.20	0.59±0.27	11.94±0.18	1.12±0.16	26.45±0.32^0
2	F2	0.52±0.26	0.68±0.25	11.22±0.29	1.11±0.21	27.49±20^0
3	F3	0.51±0.095	0.62±0.19	9.62±0.27	1.09±0.13	27.05±0.11^0
4	F4	0.68±0.12	0.69±0.20	9.67±0.22	1.12±0.19	27.52±0.27^0
5	F5	0.53±0.31	0.58±0.13	8.61±0.13	1.09±0.16	28.62±0.31^0
6	F6	0.54±0.22	0.78±0.18	26.77±0.21	1.37±0.12	30.78±0.23^0
7	F7	0.59±0.21	0.63±0.21	10.45±0.29	1.11±0.20	26.51±0.18^0
8	F8	0.61±0.11	0.72±0.15	11.27±0.18	1.19±0.13	24.38±0.28^0

The values were lies in between Bulk density 0.54 ±0.21- 0.68 ± 0.12, Tapped density 0.59 ±0.27- 0.78 ±0.27, % Compressibility 11.94 ±0.18- 27.77 ±0.21, Hausner's ratio 1.09 ±0.13 - 1.37 ±0.12, and Angle of Repose 24.38 ±0.28 - 30.78 ±0.23

Table 5: % *In vitro* Drug Release of Diltiazem Hydrochloride Microspheres

Sr.No	Time (hr)	% Drug Release							
		F1	F2	F3	F4	F5	F6	F7	F8
1	0	0	0	0	0	0	0	0	0
2	1	21.41	28.90	25.97	31.08	30.71	6.930	25.12	26.58
3	2	29.87	37.07	36.42	42.29	38.92	19.340	39.49	38.79
4	3	39.02	46.59	46.29	51.77	47.52	28.303	51.20	49.82
5	4	47.59	55.42	57.79	60.87	55.29	36.699	62.24	57.72
6	5	56.71	67.82	66.49	69.32	57.78	44.527	75.25	69.74
7	6	64.43	74.64	75.58	78.49	69.81	53.807	84.29	78.29
8	7	71.05	81.29	84.49	89.72	78.67	62.519	91.28	80.08
9	8	76.98	89.72	91.49	99.70	89.91	69.519	99.71	89.91
10	9	84.57	98.49	100.89	--	99.42	76.510	--	100.28
11	10	99.47	--	--	--	--	82.652	--	--
12	11	--	--	--	--	--	93.127	--	--
13	12	--	--	--	--	--	100.44	--	--

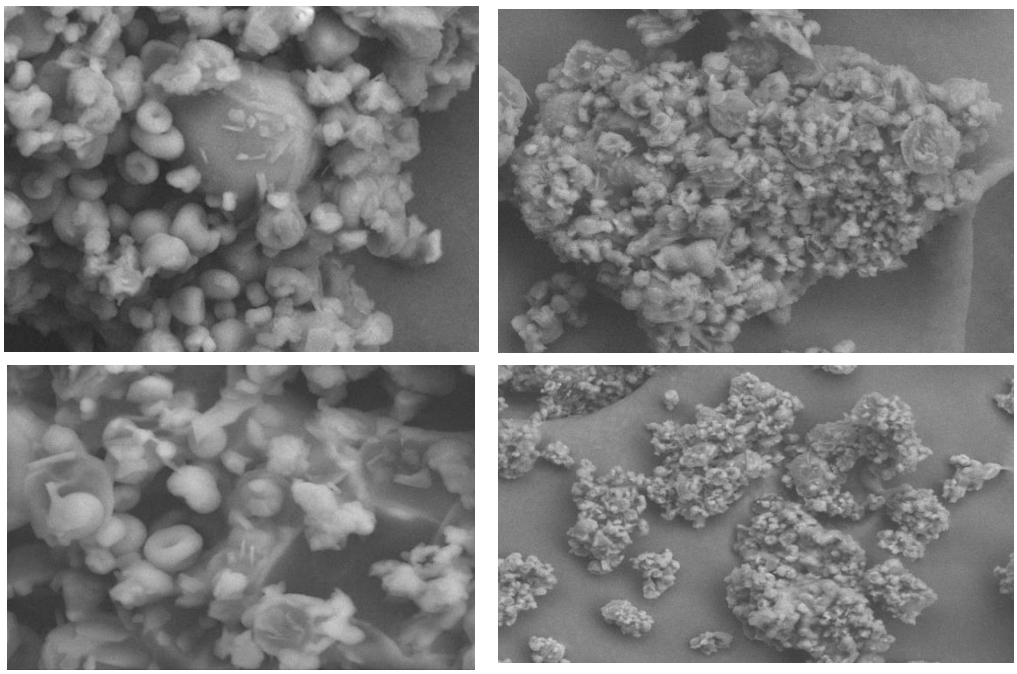

Figure 3: SEM of Diltiazem Hydrochloride Microspheres of optimized batch.

The yield of micro-encapsulation was determined by comparing the whole weight of beads formed against the combined weight of the copolymer and drug. % DEE of formulated microcapsules was found to be 90 to 99%. The optimized batch F6 gives % DEE as 99%.

Drug Content Uniformity:

All the prepared formulations show drug content uniformity in the range of 60-70% The optimized batch show drug content uniformity70%.

In vitro dissolution study:

An in vitro release study was carried out using dissolution test apparatus USP Type II (Paddle Method).

Drug Kinetic Studies:

The release data obtained from various batches was studied with respect to effect of drug: polymer ratio, diluents ratio. Dissolution data of drug from prepared in situ gel at different time periods was plotted as cumulative % drug release v/s time. The dissolution data so obtained was fitted to various kinetic models like Zero Order, First order, Higuchi, Korsmeyer - Peppas models. It was found that the optimized batch F6 follow Zero order model.

The drug release kinetics from all the batches were calculated, which was illustrated as follows-

Table 6: Kinetic Study of Diltiazem Hydrochloride Microspheres

Batch	Zero order	First order	Matrix	Peppas	Hixon crowell	Best Model fit
F1	0.5989	0.8918	0.9952	0.9852	0.6915	Matrix
F2	0.6323	0.9444	0.9449	0.8686	0.9334	Matrix
F3	0.8168	0.9940	0.9878	0.9764	0.9746	First Order
F4	0.8279	0.7227	0.3584	0.4012	0.6098	Hixon crowell
F5	0.9251	0.8219	0.9948	0.9833	0.8114	Matrix
F6	0.9979	0.8972	0.9405	0.9942	0.8439	Zero order
F7	0.9251	0.8229	0.9948	0.9833	0.8114	Matrix
F8	0.8497	--	0.7229	1.000	0.8403	Peppas

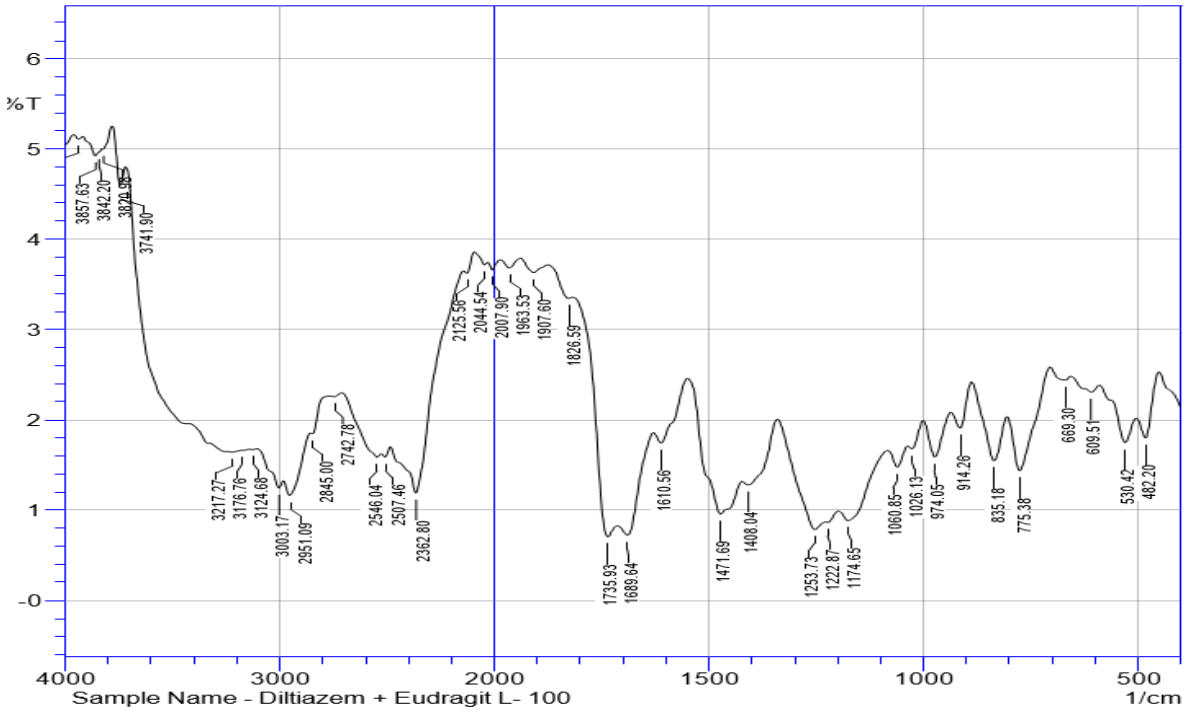

Figure 4: Interpretation of studied FTIR peaks with their Characteristics functional groups (Optimize Batch)

Interpretation of studied FTIR peaks with their Characteristics functional groups (Optimize Batch) –

1. 1735.93 cm^{-1} – Esteric – CO str
2. 2546.04cm^{-1}- Thiol
3. 3217.27cm^{-1} - -NH str
4. 2951.09cm^{-1} – Aliphatic (CH3,CH2,CH) str
5. 3003.17cm^{-1} – Aromatic CH str
6. 1735.93cm^{-1} - C=O Stretching Carboxylic acid
7. 2951.09cm^{-1} - C-H Stretching Alkanes

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