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Formulation, Evaluation and Optimization of Sustain Release Matrix Tablet of Diltiazem HCL by Using Hydrophilic Natural Polymers

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ABSTRACT

Diltiazem HCl is a Calcium channel blocker which is used as anti-anginal and Class IV anti-arrhythmic drug. It is a drug of choice for stable and unstable angina pectoris, myocardial infarction, coronary artery spasm, cardiac arrhythmia, PSVT and hypertension. In this study, sustained release matrix tablets of Diltiazem HCl were prepared by wet granulation method. The formulation of each Diltiazem HCl sustained release matrix tablets is composed of two selected polymers i.e. chitosan and xanthan gum in alone or in combination. The other excipients used were lactose monohydrate for its diluent property, PVP K-30 as a binder and magnesium stearate and talc for lubrication. The weight of tablet was adjusted to 200 mg and each tablet contained 90 mg Diltiazem HCl. Total 9 batches (F1-F9) were prepared.Batch F1, F2 and F3 containing a single polymer i.e. xanthan gum in concentration of 15, 20 and 25% of total weight of the tablet. Batch F4, F5 and F6 containing a single polymer i.e. chitosan in concentration of 20, 30 and 40% of total weight of the tablet Batch F7, F8 and F9 containing combination of both polymers i.e. xanthan gum & chitosan in concentration of proportion ratios of 15:25, 17.5:25 and 20:25% of total weight of the tablet respectively.

All the powders were passed through 100 mesh sieve after sieving. The drug & polymer were mixed uniformly, lactose was added to the above mixture and blend for 20 min. PVP K-30 dissolved in isopropyl alcohol (3%) was then added to the above mixture to form a wet mass. The wet mass was then passed through sieve no. 12 and granules were dried for 2 hrs at 55-600C. After drying, granules were passed through 16 mesh screen and resulting granules were mixed with magnesium stearate (1%) and talc (2%). The lubricated granules were compressed using flat faced punches (single punch tablet machine) into tablets. Compression pressure was adjusted during tableting of each formula to get the tablet hardness in the range of 6 to 6.5 kg/cm2. The compressed tablets of each formulation batch were then evaluated for tablet

characteristics such as thickness, hardness, weight variation, friability and drug content. In this work showed that the drug release profile of formulation F8 resembles with that of marketed formulation. Hence formulation F8 containing combination of Xanthan gum and Chitosan in the concentration ratio of 17.5:25% (of the total weight of tablet) was considered as optimized formulation.

Keywords : Diltiazem HCl; wet granulation method, Sustain release matrix tablet, Spray drying technique, chitosan and xanthan gum, dissolution rate

I. INTRODUCTION

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been employed for the systemic delivery of drug via various pharmaceutical products of different dosage forms. For sustained as well as controlled drug delivery system, the oral route of administration has received the most attention, because of ease in dosage form design for oral than parenteral route, quite high patient acceptance, relatively safe route of drug administration and minimal damage at the site of administration. An ideal or advanced drug delivery system is that, which precisely control the rate, time and/or site of drug delivery independently of normal physiological variables such as pH of GI tract, digestive state of GI tract, peristaltic movement and circadian rhythm.

Rationale of Sustained and Controlled Drug Delivery

The basic rationale for controlled drug delivery is to alter the pharmacokinetic and pharmacodynamic properties of pharmacological active moieties by using novel drug delivery system or by modifying the molecular structure and pharmacological parameters inherent in the selected route of administration. It is desirable that the duration of drug action becomes more a desiring property of rate controlled dosage form and less or not at all a property of the drug molecule inherent kinetics properties. Thus optional design of controlled release systems necessitates a thorough understanding of the pharmacokinetic and pharmacodynamic properties of the drugs.

Sustained Release Dosage Forms:

It is defined as any drug delivery system that achieves slow release of drug over an extended period of time. It provides a prolonged but not uniform release of drug and reduces the need of repeated dosing. Sustained release technology is relatively new field and as a consequence, research in the field has been extremely fertile and has produced many discoveries. Controlled release dosage form are the systems from which drug is released from the system in a planned, predictable and slower than conventional manner. With many drugs, the basic goal is to achieve a steady state blood level that is therapeutically effective and non-toxic for an extended period of time. Sustained release, sustained action, prolonged action, controlled release, extended action, timed release and depot dosage form are systems that are designed to achieve prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a unit dose. In case of oral sustained release dosage forms, an effect is for several hours depending upon residence of formulation in GI

tract. Not all the drugs are the suitable candidates for the sustained release dosage form.

Ideal characteristics of the drug for the sustained release dosage forms are -

- Drug should have a shorter half-life as drugs with a longer half-life are inherently long acting.
- Drug should be absorbed form large portion of GI tract, since absorption must occur through the gut.
- Drug should be having a good solubility profile to be a good candidate for sustained release dosage form.
- Dose of the drug should not be too large, as a larger dose is difficult to be incorporated into sustained release dosage form.

Advantages:

- Improves patient compliance due to reduced frequency of dosing.
- Uniform level of drug in blood level is maintained.
- Lower dose requirement.
- Minimize or eliminate local or systemic side effects.
- Minimize drug accumulation with chrome dosing.
- Obtained less potential of reduction in drug activity with chronic use.
- Improved efficiency in treatment.
- Cure or control condition more promptly.
- Improved control of condition i.e. reduced fluctuation in drug level.
- Improves bioavailability of some drugs.
- Make a use of special effects, e.g. sustained release aspect for relief of arthritis by dosing before bedtime.
- Economy
- Overall, administrations of sustained release form enable increased reliability of therapy.

Disadvantages:

- Dose dumping which may leads to severe toxicity
- Reduced potential for accurate dose titration
- Increased potential for first pass metabolism and also poor systemic availability.
- Stability problems and need for additional patient education.
- Effective drug release period is influenced & limited by GI residence time.
- Recovery of drug from the body is difficult in case of toxicity.
- Slow absorption may delay the onset of action.
- The remaining matrix must be removed after the drug has been released.
- The drug release rates vary with the square root of time. Release rate continuously diminishes due to an increase in diffusional resistance and/or a decrease in effective area at the diffusion front.
- However, a substantial sustained effect can be produced through the use of very slow release rates, which in many applications are indistinguishable from zero-order.

Sustained Release Matrix Systems:

The matrix system is most often used for controlled drug release from pharmaceutical dosage forms. It is the system which delay and control release of the drug that is dissolved or dispersed in a resistant support to disintegration.

A matrix device consists of drug dispersed homogenously throughout a polymer matrix. To define a matrix, it is necessary to know the characters that differentiate it from other controlled release dosage forms. Hence the following must be considered-

1. Chemical nature of support (support formed by polymeric net).
2. Physical state of drug (dispersed under molecular or particulate form or both)

3. The matrix shape and alteration in volume as a function of time.
4. The route of administration
5. The release kinetic model.

Classification of Matrix Tablets:

A. On the Basis of Retardant Material Used:

Matrix tablets can be divided in to five types:

1. Hydrophobic Matrices (Plastic matrices): Drug is mixed with an inert or hydrophobic polymer and then compressed into a tablet. Sustained release is produced due to the fact that the dissolving drug has diffused through a network of channels that exist between compacted polymer particles e.g. polyethylene, polyvinyl chloride, ethyl cellulose and acrylate polymers and their copolymers. The rate-controlling step is liquid penetration into the matrix. The possible mechanism of release of drug in such type of tablets is diffusion i.e. non- lipidic drug delivery by diffusion. Such types of matrix tablets become inert in the presence of water and gastrointestinal fluid.

2. Lipid Matrices: These matrices prepared by the lipid waxes and related materials. Drug release from such matrices occurs through both pore diffusion and erosion. Release characteristics are therefore more sensitive to digestive fluid composition than to totally insoluble polymer matrix. Carnauba wax in combination with stearyl alcohol or stearic acid has been utilized for retardant base for many sustained release formulation.

3. Hydrophilic Matrices: The formulation of the drugs in gelatinous capsules or more frequently, in tablets, using hydrophilic polymers with high gelling capacities as base excipients, is of particular interest in the field of controlled release. Intact, a matrix is defined as well mixed composite of one or more drugs with a gelling agent (hydrophilic polymer). These systems are called swellable controlled release systems. The polymers used in the preparation of hydrophilic matrices are divided into three broad groups

1. Cellulose derivatives: methylcellulose 400 and 4000 cps; hydroxyethylcellulose; hydroxypropylmethylcellulose (HPMC) 25, 100, 4000 and 15000 cps; and sodium carboxymethylcellulose.

2. Non-cellulose natural or semi synthetic polymers: agar-agar; carob gum; alginates; molasses; polysaccharides of mannose and galactose; chitosan and modified starches.

3. Polymers of acrylic acid; carbopol 934, the most used variety.

4. Biodegradable Matrices: These consist of the polymers which comprised of monomers linked to one another through functional groups and have unstable linkage in the backbone. They are biologically degraded or eroded by enzymes generated by surrounding living cells or by nonenzymatic process into oligomers and monomers that can be metabolized or excreted.

e.g. natural polymers such as proteins and polysaccharides; modified natural polymers; synthetic polymers such as aliphatic poly (esters) and poly anhydrides.

5. Mineral Matrices: Drug is either retained in the support or absorbed on the support**.** These consist of polymers which are obtained from various species of seaweeds.

E.g. Alginic acid which is a hydrophilic carbohydrate obtained from species of brown seaweeds (Phaephyceae) by the use of dilute alkali.

B. On the Basis of Porosity of Matrix:

Matrix system can also be classified according to their porosity such as macroporous, microporous and non-porous systems:

1. Macro porous System: In such systems the diffusion of drug occurs through pores of matrix, which are of size range 0.1 to 1 μm. This pore size is larger than diffusant molecule size.

2. Micro porous System: Diffusion in this type of system occurs essentially through pores. For microporous systems, pore size ranges between 50 –

200 A°, which is slightly larger than diffusant molecules size.

3. Non-porous System: Non-porous systems have no pores and the molecules diffuse through the network meshes. In this case, only the polymeric phase exists and no pore phase is present.

Advantages of Matrix System:

- With proper control of manufacturing process, reproducible release profiles are possible.
- No risk of dumping of large part of dose
- Large capacity to incorporate the active principle.
- Safety margin of high-potency drugs can be increased.
- Drug release from hydrophilic matrices show a typical time dependent profile i.e. decreased drug release with time because of increased path length.

1.7 Mechanisms of Drug Release from Matrix Systems:

I. Dissolution controlled release

Sustained release oral products employing dissolution as the time limiting step are simplest to prepare. If a drug has a rapid rate of dissolution it is possible to incorporate it into a tablet with a carrier that has a slow rate of dissolution. In the dissolution process if the dissolution process is diffusion layer control, the rate of diffusion of drug from the solid surface to the bulk solution through an unstirred liquid film, is the rate limiting step. In this case the dissolution process at steady state would be described by Noyes-Whitney equation

$dc/dt = KDA (Cs-C)$ …….(1)

Where,

dc/dt dissolution rate.

KD dissolution rate constant.

Cs saturation solubility of drug

C the concentration of drug in bulk of the solution.

In relation to diffusion expression, that

$KD = D/v \times I$ …….. (2)

Where

D dissolution coefficient

V volume of dissolution media

I the thickness of unstirred liquid film.

From the above expression it can be seen that rate of dissolution i.e. availability is approximately proportional to the solubility of the drug in the dissolution media i. e. (Cs) provided a constant area and diffusion path length are maintained. This equation predicts constant dissolution rate as long as enough drug is present to maintain Cs constant, provided surface area does not change.

Dissolution control formulations are categorized as

a. Encapsulation dissolution control

b. Matrix dissolution control.

a. Encapsulation dissolution control

This method involves coating individual particles or granules of drug with slowly dissolving material. The coated particles can be compressed directly into tablet as in space tabs or placed in capsule as in spansule products.

b. Matrix dissolution control

This method involves compression of the drug with a slowly dissolving carrier in a tablet form. Here the rate of drug availability is controlled by the rate of penetration of the dissolution fluid into the matrix. This in turn, can be controlled by porosity of the tablet matrix, the presence of hydrophilic polymer and the wettability of the tablet and particles surface.

II. Diffusion controlled release

These systems are of two types.

1. Encapsulation diffusion control

In this system water-insoluble polymeric material encases a core of drug. Drug will partition into the polymer membrane and exchange with the fluid surrounding the particle or tablet.

The rate drug release is given by the equation.

$dm/dt = ADK\Delta C$ ……. (3)

Where,

A is area

D is diffusion coefficient

K is the partition coefficient of the drug between the membrane and the drug core

I is the diffusional path length

ΔC is the concentration difference across the membrane.

An important parameter in the above Eq (3) is the partition coefficient, which is defined as the concentration of the drug in the membrane over the concentration of the drug in core.

2. Matrix Diffusion Control

In this system, a solid drug is dispersed in lipophilic or a hydrophilic polymer matrix and the rate of release of drug depends on the rate of drug diffusion and not on the rate of solid dissolution.

1.8 Factors Affecting Drug Release from Matrix Systems:

1. Choice of matrix material
2. Amount of drug incorporated in matrix
3. Viscosity of hydrophilic material in aqueous system at a fixed concentration
4. Drug : polymer ratio
5. Tablet hardness, porosity and density variation.
6. Entrapped air in tablets
7. Tablet shape and size
8. Drug particle size
9. Solubility of drug aqueous phase
10. Surfactants and other additives.
11. Hydrophilic Natural Gums

Abnormal automaticity or impaired conduction or both underlie cardiac arrhythmias. Ischemia, electrolyte and pH imbalance, mechanical injury and drug influences can cause arrhythmias by altering electro-physiological properties of cardiac fibres. Anti-arrhythmics are the drugs used to prevent or treat irregularities of cardiac rhythm. They are classified as Membrane Stabilizing Agents (Na^+ channel blockers), Anti-adrenergic Agents (β blockers), Agents widening AP (prolong repolarization and ERP) and Calcium Channel Blockers.

Calcium Channel blockers

These are the drugs that block cellular entry of Ca^{2+} through calcium channels rather than its intracellular actions. These agents are a chemically and pharmacologically heterogeneous group of synthetic drugs, but they possess the common property of selectively antagonizing Ca^{2+} movements that underlie the process of excitation–contraction coupling in the cardiovascular system. The primary use of these agents is in the treatment of angina, selected cardiac arrhythmias, and hypertension.

Although the Ca^{2+} channel blockers are potent vasodilating drugs, they lack the fluid-accumulating properties of other vasodilators and the persistent activation of the sympathetic and renin–angiotensin–aldosterone axes. Furthermore, the broad potential range of activities, both within and without the cardiovascular system, suggests that they may be clinically useful in disorders from vertigo to failure of gastrointestinal smooth muscle to relax.

Types of Calcium Channels:

a) Voltage Sensitive Channels:

Activated when membrane potential drops to -40 mV or lower. Voltage Sensitive Channels are heterogonous in nature and three types of Voltage Sensitive Channels are

- L-type channels (long lasting current)
- T-type channels (Transient current)
- N-type channel (Neuronal).

b) Receptor Operated Channels:
Activated by adrenaline and other agonists, independent of membrane depolarization.

c) Leak Channels:
Small amount of Ca^{2+} leak into the resting cell and are pumped out by Ca^{2+}ATPase.
Only the voltage sensitive L-type channels are blocked by calcium channel blockers.
The important classes of Calcium Channel blockers (CCBs) are exemplified as

1) Dihydropyridines e.g. Nifedipine, Amlodipine, Felodipine
2) Phenylalkylamines e.g.Verapamil
3) Benzothiazepines e.g. Diltiazem.

Mechanism of Action:
Drugs of each of the three chemical classes mentioned above all bind to the α_1-subunit of the cardiac L-type calcium channel but to distinct sites, each of which interacts allosterically with each other and with the gating machinery of the channel, indirectly preventing diffusion of Ca^{2+} through its pore in the open channel. Many calcium antagonists show properties of use-dependence (i.e. they block more effectively in those cells in which the calcium channels are most active). For the same reason, they also show voltage-dependent blocking actions, blocking more strongly when the membrane is depolarized, causing calcium channel opening and inactivation.

Uses:
Calcium Channel blockers (CCBs) are mainly used in the following conditions,
a) Angina pectoris; mainly effective in classical and variant angina. CCBs helps to reduce cardiac work due to reduced after load.
b) Myocardial infarction; Diltiazem and Verapamil employed for prophylaxis.
c) Hypertension; CCBs are first-line drugs for hypertension.
d) Cardiac Arrhythmias: Diltiazem and Verapamil are highly effective in Paroxysmal Supraventricular tachycardia (PSVT), for the control of Ventricular rate in Supraventricular arrhythmia.
f) Hypertrophic cardiomyopathy.

II. Materials and methods

2.1. Materials

Diltiazem HCl were obtained as a gift sample from SVK Laboratories Pvt. Ltd, Hyderabad. Xanthan Gum, Chitosan from Swapnroop Drugs Pvt. Ltd.mumbai. Lactose monohydrate, Magnesium Stearate from Merck Chemicals Ltd., Mumbai and other excipients from Fine Chemical, Mumbai

2.2 Preparation of matrix tablets by Wet Granulation method

The sustained release matrix tablets of Diltiazem HCl were prepared by wet granulation method. Table No. 1 shows the composition of each matrix formulation. All the powders were passed through 100 mesh sieve after sieving. The diltiazem HCl & polymer were mixed uniformly, lactose was added to the above mixture and blend for 20 min. PVP K-30 dissolved in isopropyl alcohol (3%) was then added to the above mixture to form a wet mass. The wet mass was then passed through sieve no. 12 and granules were dried for 2 hrs at 55-60^{0}C. After drying, granules were passed through 16 mesh screen and resulting granules were mixed with magnesium stearate (1%) and talc

(2%). The lubricated granules were compressed using flat faced punches (single punch tablet machine) into tablets. Compression pressure was adjusted during tableting of each formula to get the tablet hardness in the range of 6 to 6.5 kg/cm^2. Then prepared formulation was crushed & passes through further studied for evaluation tests.

2.3 Evaluation of prepared tablets:

a. Hardness

Although hardness test is not an official, tablet should have sufficient handling during packing and transportation. Hardness of tablet was measured using Monsanto hardness tester. It is the pressure required to fracture diametrically placed tablets by applying the force. The hardness of 6 tablets, from each batch was determined and hardness was taken into account, which was expressed in kg/cm^2.

b. Weight variation test:

Weighing 20 tablets individually, calculating the average weight and comparing the individual tablet weight to the average USP weight variation test. The table No.2 given below shows the weight variation tolerance for uncoated tablets.

c. Friability:

Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator was used for the purpose. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at distance of 6 inches with each revolution. Pre-weighed sample of tablets was placed in the friabilator, which was then operated for 100 revolutions. Tablets were dusted and re-weighed. Compressed tablets should not lose more than 1% of their weight.

The percentage friability was measured using the formula,

$$\% F = \{1-(Wo/W)\} \times 100$$

Where,

% F = friability in percentage

Wo= Initial weight of tablet

W= weight of tablets after revolution

d. Content Uniformity:

For this at least 30 tablets were randomly selected. Out of 30 tablets, 10 tablets were crushed into fine powder and assayed individually; the tablet should be within 85% to 115% of the labeled claim.

e. Thickness:

The thickness of the tablet was measured using Vernier caliper. Thickness of five tablets from each batch was measured and mean was calculated.

f. *In-Vitro* Drug Release Studies of Formulated Tablets:

In-vitro drug release studies of Diltiazem HCl matrix tablets were carried out using six station USP type II Dissolution Testing Apparatus (6 vessel assembly, Paddle type) at 75 rpm. The dissolution medium consisted of 900 ml of 1.2 pH buffer (0.1 N HCl) for first 2 hours. Then 900ml of pH 7.4 phosphate buffer for remaining period of study. Temperature was maintained at 37±0.5^{0}C. Aliquots of 5ml were withdrawn at predetermined time intervals & an equivalent amount of fresh dissolution fluid equilibrated at the same temperature was replaced. Aliquots were filtered through wattman filter paper, suitably diluted using each dissolution media (1.2 pH buffer and phosphate buffer pH 7.4) and analyzed spectrophotometrically at 236nm.

Profile of Marketed Formulation:

DILZEM (SR tablet, contains 90 mg Diltiazem HCl)

Manufactured by: Torrent Pharmaceuticals Ltd.

III. Result and Discussion

In the present work a successful attempt was made to achieve sustained release matrix tablets of Diltiazem HCl were prepared by wet granulation method. FTIR spectra of diltiazem HCl and polymer were scanned over the wavenumber range of 4000 to 500 cm $^{-1}$ .The principal peaks for Diltiazem HCl were obtained at wave no.3700, 1700, 3000, 2500, and 1800-600 cm $^{-1}$. No significant changes in peak pattern in the IR spectra of pure diltiazem HCl and physical mixtures of drug with polymer indicates that there is no interaction between pure diltiazem HCl and polymer. Tablets of all formulations (F1 to F9) were evaluated for different parameters such as thickness, hardness, weight variation, drug content and friability and results shown in table no. 3.Tablet hardness was determined by using Monsanto hardness tester. Hardness of three tablets of each tablet was determined. Hardness values of the formulation ranged from 6 to 6.5 kg/cm2, which indicate good strength of tablet. Tablet friability was determined by Roche friabilator and weight loss was calculated and represented in the terms of % friability. Friability values of all the formulation were less than 1%, indicating good strength of tablet. In weight variation test, the Pharmacopoeial limit for percent of deviation for tablets weighing between 130-324 mg is not more than 7.5%. The average percent deviation of all tablets was found to be within the limit and hence all formulation passes the weight variation test. Examination of tablets from each batch showed flat circular shape with no cracks having white colour. The thickness of tablets was determined using Vernier caliper. The thickness of tablets ranged from 2.4±0.03mm to 2.8±0.07mm. All formulations showed uniform thickness. The drug content was found to be uniform among all formulation and ranged from 98.23% to 101.93%.

The in-vitro drug release characteristics were studied in pH 1.2 buffer (0.1 N HCl) for first two hours and in phosphate buffer pH 7.4 for next 10 hours under sink condition using USP dissolution apparatus type II. The theoretical release profile calculation is important to evaluate the formulation with respect to release rates and to ascertain whether it releases the drug in predetermine manner.

IV. Conclusion

Amorphous solid mixture of Telmisartan was successfully prepared by Solvent evaporation technique and spray drying technique using adsorbents carrier and diluents. Excipients were selected on the basis of nonirritating and non toxic properties. The adsorbents carrier increases the water solubility and dissolution profile of Telmisartan. The solid state studies confirmed that amorphization of adsorbents with an adsorbents carrier by decreasing crystallinity and there is no any chemical interaction. The Solvent evaporation method prepared was found to be satisfactory as it produced good product with high drug content. It shows significant improvement of the in vitro dissolution rate. In Vitro dissolution study by using 0.1N HCL as a media shows that Solvent evaporation mehod of optimized batches give faster dissolution rate. The research work has shown increase in solubility of Telmisartan with increase in dissolution rate may be attributed to increase surface area due to use of absorbent carrier. A result of stability study concludes the formulated mixture was stable enough at 40 0 C2°C/75 5% RH for 1 month.

V. Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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AUTHOR CONTRIBUTION STATEMENT

Mr. Sharad Kamble conceptualized and gathered the data with regard to this work. Mrs. Sunita Shinde analyzed these data and necessary inputs were given towards the designing of the manuscript. All authors discussed the methodology and results and contributed to the final manuscript.

Declaration of interests

☐✓ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ ✓ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests

Table(s)

Table 1. Formulation Chart of Diltiazem HCl matrix tablets

Batch/ Ingredients (mg)	Drug	Xanthan gum	Chitosan	Lactose	PVP	Mg. stearate	Talc	Total weight
F1	**90**	**30**	**-**	**74**	**3**	**2**	**1**	**200**
F2	**90**	**40**	**-**	**64**	**3**	**2**	**1**	**200**
F3	**90**	**50**	**-**	**54**	**3**	**2**	**1**	**200**
F4	**90**	**-**	**40**	**64**	**3**	**2**	**1**	**200**
F5	**90**	**-**	**60**	**44**	**3**	**2**	**1**	**200**
F6	**90**	**-**	**80**	**24**	**3**	**2**	**1**	**200**
F7	**90**	**30**	**50**	**24**	**3**	**2**	**1**	**200**
F8	**90**	**35**	**50**	**19**	**3**	**2**	**1**	**200**
F9	**90**	**40**	**50**	**14**	**3**	**2**	**1**	**200**

Table 2. Weight variation tolerance for uncoated tablets

Average Weight of Tablet (Mg)	Maximum % Deviation Allowed
130mg or less	10%
130mg to 324mg	7.5%
More than 324mg	5%

Table 3. Evaluation Tests of Matrix Tablets

Formulation	Hardness (kg/cm^2) (Mean±S.D)	Percent friability (%) (Mean±S.D)	Thickness (mm) (Mean±S.D)	Content uniformity (%) (Mean±S.D)	Weight variation (Mean±S.D)
F1	6.3±0.1	0.57±0.03	2.8±0.02	101.93%	200.66±0.57
F2	6.5±0.3	0.68±0.01	2.5±0.06	98.86%	199.34±1.1
F3	6.2±0.2	0.49±0.04	2.4±0.03	99.28%	201.25±0.68
F4	6.1±0.2	0.65±0.02	2.7±0.02	98.77%	201.91±1.13
F5	6.4±0.4	0.51±0.06	2.6±0.04	99.81%	202.11±1.15
F6	6.2±0.3	0.62±0.04	2.8±0.07	100.47%	199.37±0.88
F7	6.4±0.2	0.67±0.06	2.4±0.06	98.23%	201.53±0.35
F8	6.5±0.2	0.69±0.03	2.7±0.08	99.76%	200.54±0.68
F9	6.4±0.1	0.55±0.05	2.6±0.04	99.21%	200.45±0.84

Table 4. *In-vitro* dissolution data of F1, F2, F3 & Marketed formulation

ne in ours	% Cumulative drug release (mean ± S.D.)			
	F1	F2	F3	Marketed
0	00.00	00.00	00.00	00.00
1	3.6±0.421	0.6±0.474	9.45±0.652	7.78±0.563
2	3.2±0.547	8.0±0.659	7.14±0.455	5.58±0.452
3	2.0±0,345	5.1±0.239	4.65±0.316	3.76±0.544
4	0.48±0.473	.74±0.596	0.61±0.276	1.08±0.511
5	8.9±0.431	.35±0.461	46.5±0.233	9.47±0.288
6	8.5±0.499	5.91±0.321	3.21±0.549	7.32±0.324
7	7.4±0.376	3.33±0.769	0.22±0.671	4.11±0.672
8	5.05±0.612	0.21±0.377	6.28±0.429	1.30±0.459
9	.34±0.433	5.75±0.563	2.76±0.434	9.36±0.395
10	7.3±0.376	3.28±0.663	8.41±0.546	7.34±0.432
11	-	0.31±0.245	3.89±0.265	3.29±0.451
12	-	5.90±0.543	90.7±0.653	8.24±0279

Figures

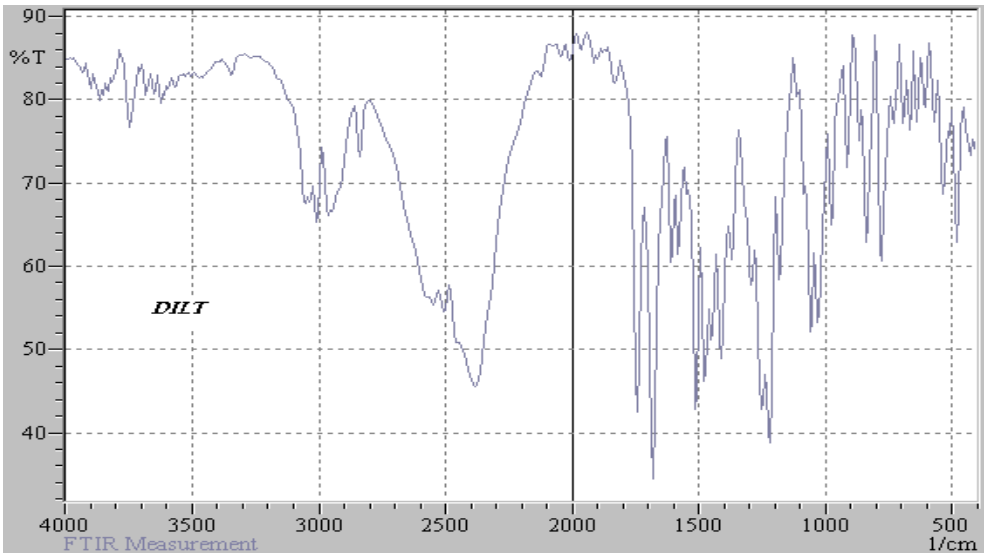

Fig. No. 1: IR Spectra of Diltiazem HCl

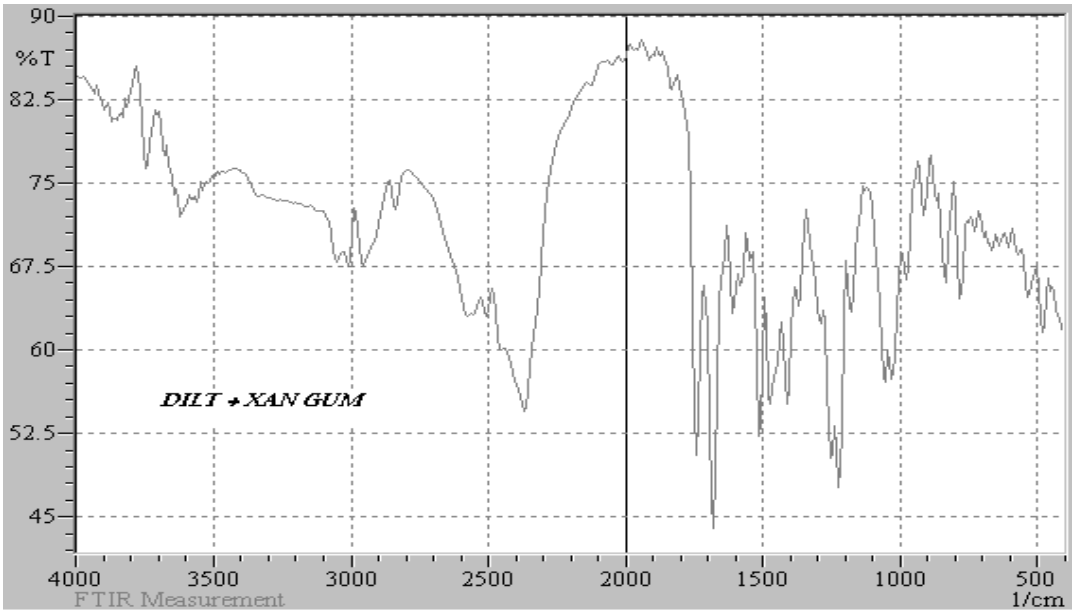

Fig. No. 2: IR Spectra of Diltiazem HCl with Xanthan gum

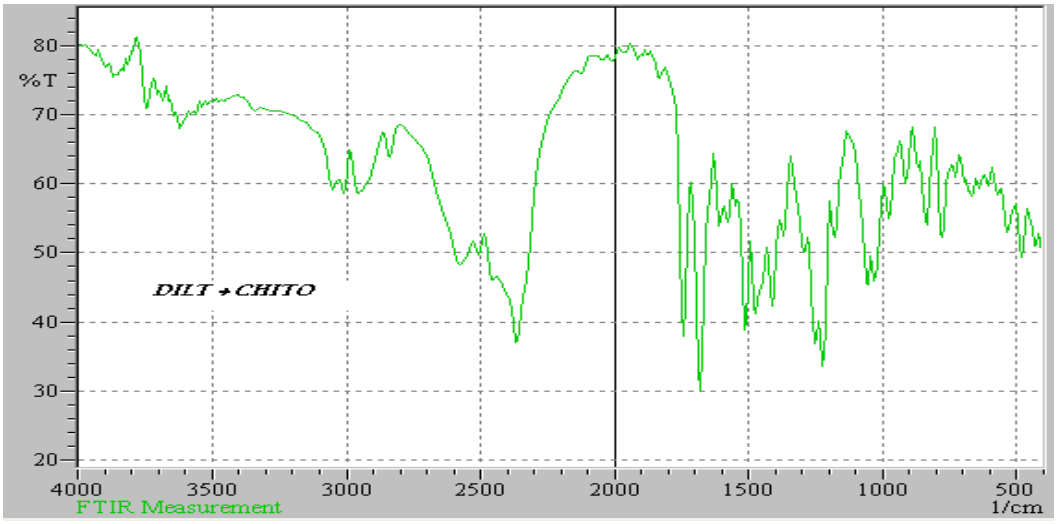

Fig. No. 3: IR Spectra of Diltiazem HCl with Chitosan

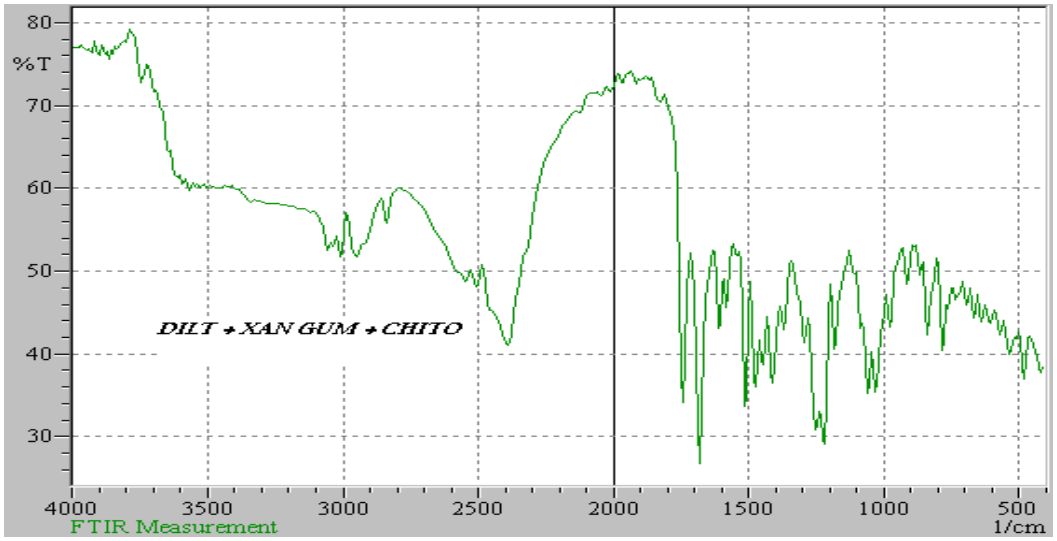

Fig. No. 4: IR Spectra of Diltiazem HCl with chitosan & xanthan gum