

Research Article

Preparation and Evaluation of Sustained Release Drug Delivery of Diltiazem Hydrochloride.

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ABSTRACT

Matrix tablets using PEC as matrix and Diltiazem HCl as a model drug were formulated by wet granulation technique. The matrix tablets were evaluated for physical properties, in vitro release and release data analysis. The maximal yield was obtained when the ratio of guar gum: pectin was 3:7 (w/w). Release kinetic was evaluated by using USP XXIV dissolution apparatus type II was 89.54 %. It was concluded from the study that guar-pectin binary polymeric matrix system is an interesting alternative for preparing sustained release tablets.

KEYWORDS

Diltiazem HCl, Sustained Release Drug Delivery.

1. INTRODUCTION

Diltiazem hydrochloride is a calcium channel antagonist widely used in the treatment of angina pectoris, systemic hypertension and supra ventricular arrhythmias. It is a highly soluble, highly permeable drug with extensive and highly variable hepatic first pass metabolism following oral administration. The development of sustained release formulation of Diltiazem hydrochloride is therefore therapeutic relevance and can be used to provide a consistent dosage through sustaining an appropriate level of the drug over time ^[1- 2]. Hydrophilic polymer matrix systems are widely used in oral sustained drug delivery because of their flexibility to obtain a desirable drug release profile, cost effectiveness, and broad regulatory acceptance. The ability of the hydrophilic polymer matrices to release and entrapped drug in aqueous medium and to regulate the release of such drug by control of swelling and cross linking makes them particularly suitable for sustained release application. Natural polysaccharide and their derivatives (like sodium alginate, agar beads, carrageenan, chitosan, pectin, guar gum, karaya gum etc.) represent a group of polymer widely used in pharmaceutical dosage forms ^[3-5]. Pectin (high methoxylated) is important ionic polysaccharides found in plant cell walls. They contain linear chains of (1-4)-linked α -D galacturonic acid residues. Its gelling ability and solubility strongly depends upon the pH of the surrounding media. The non-toxicity and the low production cost of pectin make them of great interest for the formulation of controlled release dosage forms. Guar gum is an interesting polymer for the preparation of hydrophilic matrix tablets because of its high water swellability, non toxicity and low cost. Various groups of workers have used guar gum as a controlled release carrier ^[6-7].

2. MATERIALS AND METHODS

Diltiazem Hydrochloride (M/S Koprán Ltd., Mumbai), chitosan and pectin CP Kelco, Lactose, Starch and Emcompress were procured from (S. D. Fine Chemicals, Mumbai). All other chemicals purchased and were of analytical grade.

2.1. Preparation of Matrix Tablets

Matrix tablets were prepared by wet granulation method using pectin and guar gum as per the formula given in the table 1. Diltiazem hydrochloride, pectin and, guar gum were mixed and the mixture was passed through the mesh #60. Granulation was done using sufficient quantity of granulating agent (distilled water) to get wet mass. The wet mass was passed through mesh #14. The wet granules were dried at 55⁰ for 120 minute in an oven. The dried granules were then sized by mesh #18 and mixed with magnesium stearate. The granules of Diltiazem hydrochloride were compressed by a single punch tableting machine with 13mm flat shaped punches. These formulation of same diluents i.e. lactose but with 3 different proportion were prepared.

Table 1. Different formulations of Diltiazem Hydrochloride sustained release matrix tablet.

Sr. No.	Ingredients (mg.)	A1	A2	A3
1.	Diltiazem HCL	120	120	120
2.	Pectin	240	Nil	120

3.	Gaur gum	Nil	240	120
4.	Lactose	36	36	36

2.2. Evaluation of Tablet properties

The prepared matrix tablets were evaluated for uniformity of weight, hardness, friability and thickness. Uniformity of weight was performed according to official method. Hardness of the tablets was tested using a Monsanto hardness tester. Friability of the tablets was determined in a Roche friabilator and thickness was measured by Vernier caliper. Three readings were carried out and average value was noted ^[25]. The physical properties are shown,

Table 2. Physical properties of compressed tablet.

Batch No.	Weight Uniformity (mg)	Hardness (Kg/cm2)	Friability	Thickness	Drug content
A1	367	6.22	0.72	3.31	98.1
A2	366	4.22	0.81	3.35	99.23
A3	362	4.1	0.55	3.25	100.1

2.3. Determination of drug content

Twenty tablets from each formulation were accurately weighed and average weight per tablet was determined. The tablets were powdered and powder equivalent to 400 mg of Diltiazem hydrochloride was accurately weighed and extracted four times with 20ml portions of distilled water. The extract was filtered through Whatman filter paper no. 41 into 100 ml volumetric flask and volume was made up to the mark with distilled water. The solution was suitably diluted with distilled water and analyzed against blank (distilled water) for the drug content double beam spectrophotometrically at 237 nm. Results are shown in table 2.

2.4. In vitro drug release studies

The in vitro drug release studies were carried out using USP XXIV dissolution apparatus type II (paddle) at 100 rpm. The dissolution medium consisted of 0.1N HCl for the first 2 hours and the phosphate buffer pH 6.8 from 3 to 10 hours (900ml), maintained at 37°C- 0.5°C. Five ml of samples were withdrawn and analyzed spectrophotometrically at 237 nm using a UV-visible double beam spectrophotometer (V 500 Jasco Instruments, Japan) after suitable dilution. Fresh dissolution medium was replaced after each withdrawal. The study was performed in triplicate.

2.5. FTIR studies

It was used to study the interactions between the drug and polymers. The drug and polymers must be compatible to produce a stable product. Drug and polymer interaction were studied by using FTIR (Jasco Tokyo, Japan). IR spectral analysis of pure Diltiazem hydrochloride, pectin, guar gum and Diltiazem hydrochloride with pectin and guar gum were carried out by KBr pellet

method. The peaks and pattern produced by the pure drug were compared with combination of polymer.

2.6. DSC studies

Thermal study of Diltiazem hydrochloride, pectin guar gum and Diltiazem hydrochloride with pectin and guar gum were assessed by DSC. Heating of sample was done from 50 to 250°C at rate of 10°C/min. Study carried out for evaluation of compatibility of drug and polymer used using Jasco FTIR Pellets prepared by pressing sample with KBr die set.

2.7. Stability studies

The optimized Diltiazem hydrochloride formulation (batch A3) were packed and subjected to accelerated stability studies as per ICH guidelines (40°C ± 2°C & -2°C / 75%RH + 2°C RH & -2°C). The sample were withdrawn periodically (0, 15, 30, 60, 90 days) and evaluated for the different Physico-chemical parameters viz. appearance, weight variation, thickness, hardness, drug content and in vitro drug release studies.

3. RESULTS AND DISCUSSION

The physical properties of different batches of developed matrix tablet are given in table 2. The average percentage deviation of 20 tablets of each formulation was less than (5%), and hence all formulations passed the test for uniformity of weight as per official requirements (Pharmacopoeia of India 1996). The hardness of the tablets of all the formulations ranged from (4.1 to 6.22) kg/cm², friability (0.55 to 0.81 %), thickness (3.25 to 3.35 mm), and drug content (98.1 to 100.1 %) All were found within the acceptable official limits. The data obtained from in-vitro release studies for formulation batches A1 to A3 are shown in the figure 1 & 2 respectively. The cumulative percentage drug release of formulation batch A1 (drug to pectin ratio 1:2) was 99. Initially pectin controlled the drug released rate due to its high gelling property but after 3-4 hours, due to its eroding property drug release reached the level of 99.58% at the end of 6 hours. The cumulative percentage drug release of formulation batch A2 and A3 was 76.73% and 89.54 % at the end of 10 hours respectively. In batch F2 (drug to guar gum ratio, 1:2), an initial burst release may be due to uncontrolled rate of hydration. Initial slow gelling of guar gum but after 5 hour release rate become slow due to high swelling of guar gum. In batch A3 pectin used in combination with guar gum that control burst effect by promoting gelation both in radial and axial expansion and after 4-5 hour pectin maintained the release rate by acting as eroding material and controlled release rate upto 10 hr.

Table 3. Release rate of tablet.

Time (Hrs.)	A1	A2	A3
1	20.61	32.73	21.16
2	29.12	39.54	34.92
3	40.62	45.36	45.89
4	56.58	51.26	50.84

5	77.78	56.73	60.24
6	99.58	59.73	67.01
7	-	63.73	70.93
8	-	69.73	74.15
9	-	73.73	83.28
10	-	76.73	89.54

According to ICH guidelines, three months accelerated study for the optimized formulation batch F3 showed negligible change over time for the parameters like appearance, weight variation, thickness, hardness, drug content and in vitro drug release. Results are shown in table 3.

Table 4. Stability studies data on selected formulation (F3).

Time (Hr.)	Initial tablet	15 days	30 days	60 days	90 days
1	18.19	19.62	19.24	20.31	19.84
2	31.91	30.62	33.12	32.86	32.15
3	42.89	44.09	44.16	46.20	45.40
4	58.24	51.23	52.14	49.32	50.85
5	64.9	56.83	57.32	58.87	57.57
6	68.01	66.34	64.84	63.96	66.30
7	71.12	68.12	67.02	70.15	69.85
8	80.25	72.80	73.46	74.01	71.09
9	85.54	80.56	81.12	79.27	78.17
10	86.89	88.58	86.74	85.79	85.23
Drug content	100.03	100.01	99.86	99.61	99.28

3.1. IR spectral analysis

The FTIR studies of pure Diltiazem hydrochloride, pectin, guar gum and formulations containing pectin and guar gum were carried out to study the interaction between the drug and polymers used (shown in figure 3, 4, 5 & 6 respectively). -NH stretching, -CH aliphatic stretching, aromatic -CH stretching, esteric -CO stretching, -C=O stretching of pure Diltiazem hydrochloride and the Diltiazem hydrochloride sustained release tablets formulations containing pectin and guar gum were almost in the same region of wave number ranging from 3350 cm⁻¹ to 1700 cm⁻¹. The results proved that there were no significant interactions between the drug and polymer

3.2. DSC studies

DSC thermogram of pure drug Diltiazem hydrochloride, pectin, guar gum and Diltiazem hydrochloride sustained release tablet contain pectin and guar gum are shown in fig. resp. DSC thermogram of diltiazem hydrochloride showed sharp endothermic peak. DSC thermogram of diltiazem hydrochloride sustain release tablet contain pectin and guar gum shows negligible shift

in their position with some peak broadening in latter. Therefore there were no significant interaction between drug and polymer^[8-10].

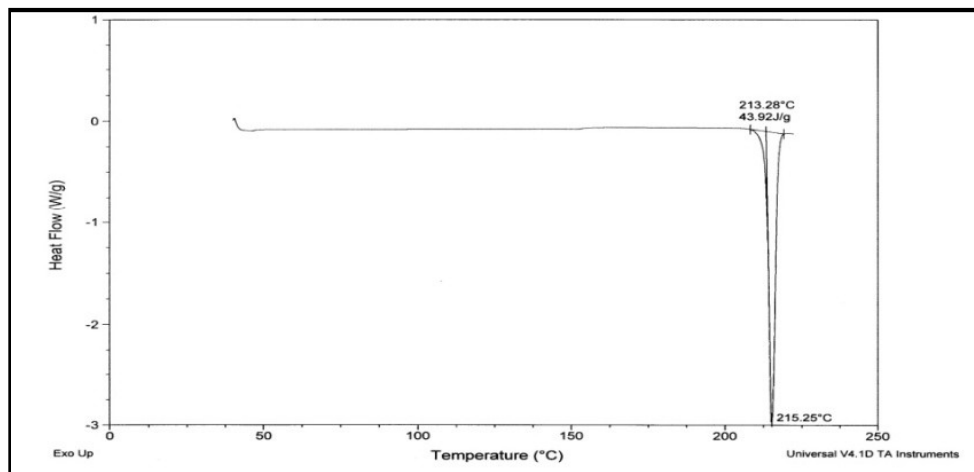


Figure 1. DSC Thermogram of Diltiazem Hydrochloride.

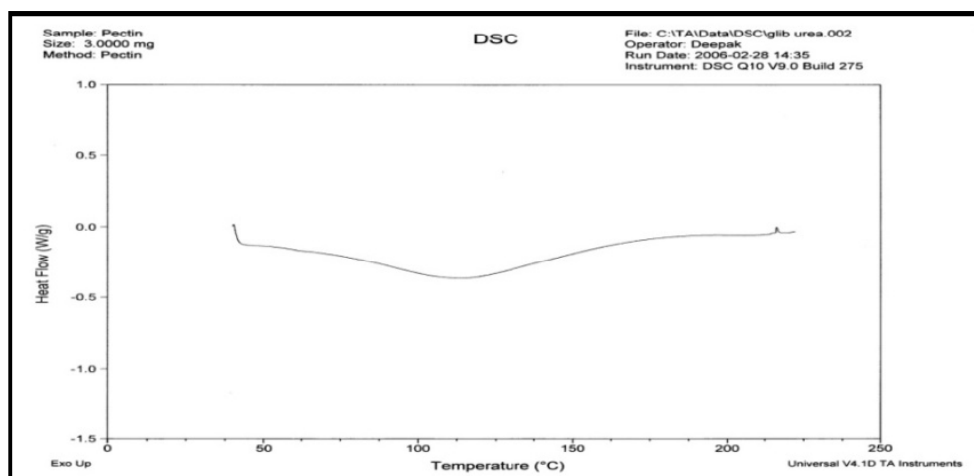


Figure 2. DSC Thermogram of Pectin.

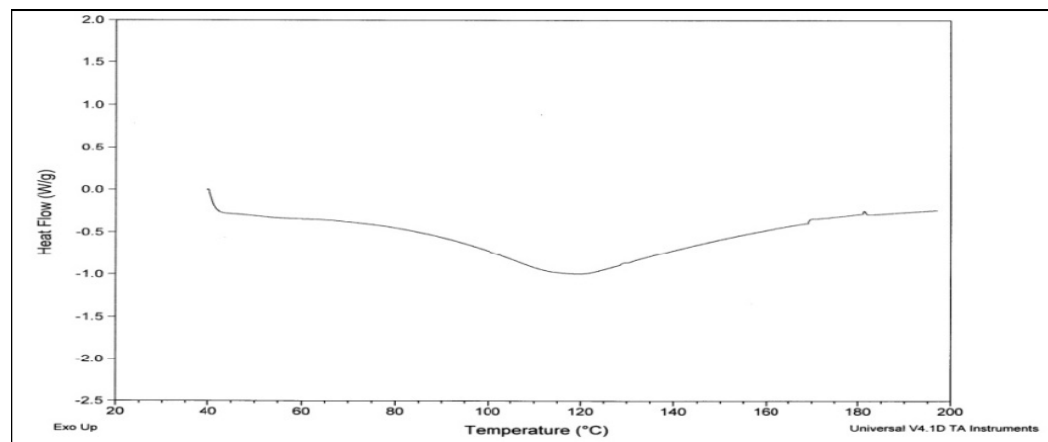


Figure 3. DSC Thermogram of guar gum.

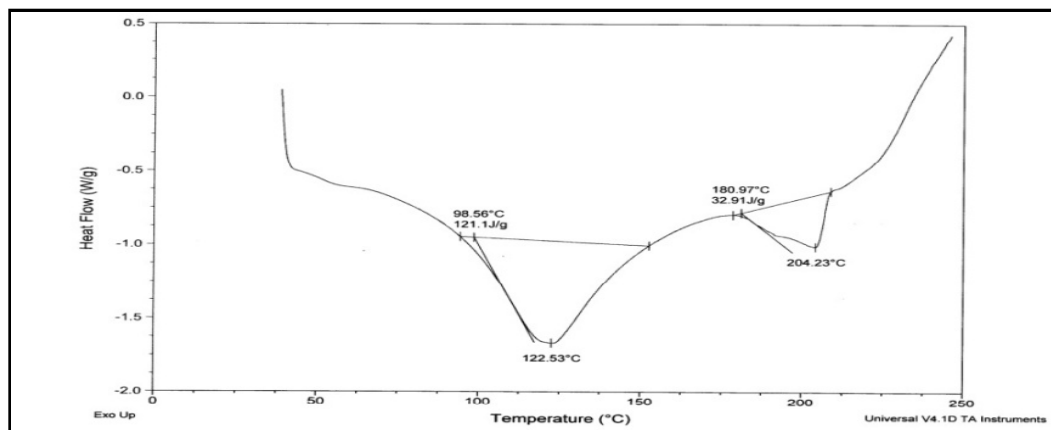


Figure 4. DSC Thermogram of Diltiazem hydrochloride with guar gum and pectin.

4. CONCLUSION

Study shows that guar gum alone cannot show efficient control drug release. When combine with pectin shows synergistic effect tin controlling the diltiazem hydrochloride release. Among formulation batch A3 shows 89.54 % release at end of 10 hours. Therefore suitable combination of two natural gum (pectin and guar gum may employed for formulating sustained release matrix tablet of Diltiazem hydrochloride.

5. REFERENCES

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