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**IN-VITRO DRUG RELEASE STUDIES OF DILTIAZEM SUSTAIN RELEASE
TABLET**

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ABSTRACT

Diltiazem is a calcium channel blocker, with half life 3 to 4.5 hours and requires multiple daily drug dosage to maintain adequate plasma concentrations. So we selected this drug to prepare a sustained release matrix tablets. The objective of this study to develop a formulation which releases the drug in a controlled manner over a period of 12 hours. The *in vitro* drug release characteristics were studied in 900ml of phosphate buffer pH 6.8 for a period of 12 hours using USP-XXIII dissolution apparatus type II (Paddle). To know the mechanism of drug release from these formulations, the data were treated according to first-order release, Higuchi's, and korsmeyer equation along with zero order release pattern. Finally we conclude that the hydrophilic matrix of HPMC alone could not control the diltiazem release effectively for 12 hours.

KEYWORDS

Diltiazem, Sustained Release, First Order Release, Higuchi's and Korsmeyer equation.

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INTRODUCTION

Controlled drug delivery systems have been developed which are capable of controlling the rate of drug deliver, sustaining the duration of therapeutic activity and/or targeting the delivery of drug to a tissue. Many terms are used to describe controlled drug delivery or modified drug delivery systems that are designed to maintain a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. These are as follows: Sustained-release, Extended-release, controlled-release, Repeat action preparation,

Delayed release preparation, site specific targeting and Receptor targeting. The concept of controlled release systems is to deliver a constant supply of the active ingredient by continuous release for a certain period of time, an amount of the drug equivalent to that eliminate by the body¹. Sustained - Release dosage formulation are the preparations provide an immediate dose require for the normal therapeutic response, followed by the gradual release of drug in amounts sufficient to maintain the therapeutic response for a specific extended period of time. The major advantage of this category is that, in addition to the convenience of reduced frequency administration, it provides levels that are devoid of the peak and valley effect, characteristic of the conventional intermittent dosage regimen².

Controlled - Release formulation are controlled release system is to deliver a constant supply of the active ingredient, usually at a zero-order rate, by continuously releasing, for a certain period of time, an amount of the drug equivalent to the eliminated by the body. An ideal controlled drug delivery system is the one, which delivers the drugs at a predetermined rate, locally or systemically, for a specific period of time. Repeat action preparations, a dose of the drug initially are released immediately after administration, which is usually equivalent to a single dose of the conventional drug formulation. After a certain period of time, a second single dose is released. In some preparation, a third single dose is released after a certain time has elapsed, following the second dose. The main *advantage* is that it provides the convenience of supplying additional dose(s) without the need of re-administration. It has *disadvantage* that the blood levels still exhibit the "Peak and valley" characteristic of conventional intermittent drug therapy.

Extended-Release formulations are usually designed to reduce dose frequency and maintain relatively constant or flat plasma drug concentration. This helps avoid the side effects associated with high concentration. Delayed release preparations, the drug are released at a later time after administration. The delayed action is achieved by the incorporation of a special coat, such as enteric coating, or other

time barriers such as the formaldehyde treatment of soft and hard gelatin capsules. The purposes of such preparations are to prevent side effects related to the drug presence in the stomach, protect the drug from degradation in the highly acidic p^H of the gastric fluid. Site specific targeting, these systems refer to targeting of a drug directly to a certain biological location. In this case the target is adjacent to or in the diseased organ or tissue. Receptor targeting, these systems refer to targeting of a drug directly to a certain biological location. In this case the target is the particular receptor for a drug with in organ or tissue. Site specific targeting and receptor targeting systems satisfy the spatial aspect of drug delivery and are also considered to be controlled drug delivery systems³. Some drugs those have relatively high solubility at the low pH with short biological half-life, are not suitable for conventional oral dosage formulations, because the high acid solubility property of drug results in rapid drug absorption and clearance, causing large and undesirable fluctuations in plasma concentration. For drugs with short half-lives and with a clear relationship between concentration and response, it will be necessary to dose at regular, frequent intervals in order to maintain the concentration within the therapeutic range. Higher doses at less frequent intervals will result in higher peak concentrations with the possibility of toxicity. For some drugs with wide margins of safety, this approach may be satisfactory, e.g. amoxicillin has a half-life of approximately one hour, but a dosage frequency of 8 hours⁴. Judicious choice of the drug substance is the most important decision in the successful development of sustained release product. Several categories of drug have potential for their therapeutics improvement of efficacy via sustained-release oral routes e.g. antianginal, Anti-inflammatory, Antihistaminic, Anti gastric resistant agents, Antipsychotic agents, Antidiabetic drugs of agents. The common goal for increased duration is twice a day, or when feasible, once a day. Several properties of the drug itself can lead to the achievement of a 12 to 24 hours oral prolonged release dosage form⁵.

MATERIAL AND METHODS

Material

Diltiazem potassium was provided Mylon, Andhra Pradesh. HPMC 15cps and Ethyl cellulose were supplied by S.D. Fine chemicals Ltd, India. Eudragit were received from Evonik Degussa India Pvt. Ltd., Mumbai.

Preparation of Diltiazem Matrix Tablets

Fifteen different tablet formulations were prepared by wet granulation technique (Formulation 1-15). The composition of 300 mg diltiazem of the drug, polymer (HPMC, CMC, NaAlg) and filler (MC) was dry mixed thoroughly and sufficient volume of granulating agent (ethanol 95%). Ethanolic solution of PVP, ERL-100, EC) was added slowly. After enough cohesiveness was obtained, the mass was sieved through 22 meshes. The granules were dried at 55°C for 1 hour. This granule mixture was blended with magnesium stearate (2%w/w) as lubricant; the appropriate and then compressed using a 16 station tablet compression machine round, flat-faced punches of 10-mm diameter and die set. All compressed tablets were stored in an airtight container at room temperature for the study⁶⁻⁷.

In-Vitro Drug Release Studies (Dissolution studies)

Dissolution Parameters

Medium: Phosphate buffer pH 6.8, Apparatus: USP-Type 2 (Paddle) RPM: 50, Temperature: 37.0 ± 0.5°C, Medium Volume: 900 ml.

Procedure

The release of diltiazem from the SR tablet was studied in 900 ml of phosphate buffer pH 6.8 as dissolution medium using a USP dissolution paddle assembly at 50 rpm and 37.0 ± 0.5°C. An aliquot (1 ml) was withdrawn at specific time intervals, filtered and diluted to 10 ml with phosphate buffer pH 6.8, and drug content was determined by UV-visible spectrophotometer at 237 nm. An equal volume of fresh dissolution medium was replaced to maintain the dissolution volume. Dissolution studies were performed 3 times for a period of 12 hrs and the mean value were taken. Cumulative percentage of drug release was calculated using an equation obtained from a standard curve⁸⁻⁹.

In-Vitro release rates of sustained release tablets of diltiazem

The results of in vitro release profile obtained for all the formulations were plotted in modes of data treatment as follows, Zero – order kinetic model – Cumulative % drug released versus time, First – order kinetic model – Log cumulative percent drug remaining versus time, Higuchi's model – Cumulative percent drug released versus square root of time, Korsmeyer equation / Peppas's model – Log cumulative percent drug released versus log time.

Zero order kinetics

Zero order release would be predicted by the following equation:- $A_t = A_0 - K_0t$ (Where, A_t = Drug release at time 't', A_0 = Initial drug concentration, K_0 = Zero – order rate constant (hr^{-1}). When the data is plotted as cumulative percent drug release versus time, if the plot is linear then the data obeys Zero – order release kinetics, with a slope equal to K^0 .

First Order Kinetics

First – order release would be predicted by the following equation: $\log C = \log C_0 - K_t / 2.303$ Where, C = Amount of drug remained at time 't'. C_0 = Initial amount of drug, K = First – order rate constant (hr^{-1}). When the data is plotted as log cumulative percent drug remaining versus time yields a straight line, indicating that the release follow first order kinetics. The constant 'K' can be obtained by multiplying 2.303 with the slope values (Figure No.2).

Higuchi's model

Drug release from the matrix devices by diffusion has been described by following Higuchi's classical diffusion equation. $Q = [D\varepsilon / \tau (2A - \varepsilon C_s) C_s t]^{1/2}$ (Where, Q = Amount of drug released at time 't', D = Diffusion coefficient of the drug in the matrix, A = Total amount of drug in unit volume of matrix, C_s = the solubility of the drug in the matrix, ε = Porosity of the matrix, τ = Tortuosity, t = Time (hrs) at which 'q' amount of drug is released. Above equation may be simplified if one assumes that 'D', ' C_s ', and 'A', are constant. Then equation becomes: $Q = Kt^{1/2}$ When the data is plotted according to equation i.e. cumulative drug release versus square root of time

yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to 'K' (Higuchi's 1963) (Figure No.3).

Korsmeyer equation / Peppas's model

To study the mechanism of drug release from the sustained – release matrix tablets of diltiazem, the release data were also fitted to the well – known exponential equation (Korsmeyer equation / Peppas's law equation), which is often used to describe the drug release behavior from polymeric systems, $M_t / M_a = Kt^n$ Where, M_t / M_a = the fraction of drug released at time 't', K = Constant incorporating the structural and geometrical characteristics of the drug / polymer system, N = Diffusion exponent related to the mechanism of the release. Above equation can be simplified by applying log on both sides, and we get: $\text{Log } M_t / M_a = \text{Log } K + n \text{ Log } t$ When the data is plotted as log of drug released versus log time, yields a straight line with a slope equal to 'n' and the 'K' can be obtained from y – intercept. For Fickian release 'n' = 0.5 while for anomalous (non – Fickian) transport 'n' ranges between 0.5 and 1.0 (Figure No.4).

RESULTS AND DISCUSSION

Diltiazem which was formulated by wet granulation method employing different concentration of polymers for sustained the release of drug, microcrystalline cellulose as diluent and magnesium stearate as lubricant and it was evaluated. To know the mechanism of drug release from these formulations, the data were treated according to first-order release, Higuchi's, and Korsmeyer equation / Peppas's model equations along with zero order (cumulative amount of drug released verses time).

In-Vitro drug release for oral sustained-release tablets of diltiazem

In vitro Release Studies¹⁰⁻¹⁴

The *in vitro* drug release characteristics were studied in 900ml of phosphate buffer pH 6.8 for a period of 12 hours using USP. XXIII dissolution apparatus type II (paddle). The results of dissolution studies indicated that F1, F2 and F3 released 99.37%, 99.59% and 99.42% of DTZ at the end of 4.5 hours,

5 hours, and 7 hours, respectively. The results of dissolution studies indicated that F4, F5 and F6 released 99.57%, 99.64% and 99.85% of DTZ at the end of 2.5 hours, 4 hours and 5.5 hours respectively. The result at dissolution studies indicated that F7, F8 and F9 released 99.43%, 99.92% and 99.11% at DTZ at the end of 2 hours, 3.5 hours and 5 hours. Among these formulations the release rate was increased in the following polymer order: Sodium alginate > CMC > HPMC. Sodium alginate and CMC released the drug at a faster rate than did HPMC. The formulation F3, which exhibited the slowest dissolution profile than other formulation. However formulation F3 were selected for further modified using different granulating agents, such as PVP, Eudragit and ethyl cellulose to control the drug release. The formulations F10 to F15 released more than 95% of DTZ at the end of 12 hours. The formulation F13 (ERL 8%) and F15 (EC 4%) exhibited the slowest dissolution than formulation F10 (PVP 5%), F11 (PVP 10%), F12 (ERL 4%) and F14 (EC 2%). The formulation F10, F11, F12 and F14 released 36.23%, 34.78%, 27.185% and 24.38% of drug at the end of 2 hour, and 98.60%, 97.79%, 97.79%, 97.8% and 97.13% of drug at the end at 12 hours respectively. These formulations showed a high release in the initial hours (Figure No.1). The formulation F13 and F14 released 25.69% and 20.93% of drug at the end of 2 hours and 95.32% and 95.38% of 12 hours respectively. From a commercial point of view, Ethyl cellulose is more economical than Eudragit. Hence, F15 is the most successful and cost-effective formulation among the matrix tablets developed in the present study (Table No.1). To know the mechanism of drug release from these formulations, the data were treated according to first-order release, Higuchi's, and korsmeyer equation / peppas's model *et al's* equation along with zero order release pattern¹⁵⁻¹⁷. The release rate kinetic data for all the other equations can be seen in Table No.1. When the data were plotted according to the first-order equation, the formulations showed a fair linearity, with regression values between 0.9503 and 0.9845 in our experiments, the *in vitro* release profiles of drug from all the formulations could be

best expressed by Higuch's equation, as the plots showed high linearity R^2 :0.9682 to 0.9948. To confirm the diffusion mechanism, the data were fit into korsmeyer, *et al*'s equation, with slope (n)

values ranging from 0.58 to 0.82. This indicates that the release of drug follows Non-Fickian transport¹⁸⁻²⁰. It means in release of drug from the tablet dissolution and diffusion both mechanisms are used.

Table No.1: In-vitro Release Profile for Diltiazem SR Tablet- Formulations (F15)

S.No	Time (Hrs)	Absorbance* (237 nm)	Concentration in mcg/ml	Amount released in mg/ml	Cumulative amount released in mg	*Cumulative % drug released
1	0	0	0	0	0	0
2	0.25	0.07573	1.8337	0.0183	16.5036	5.50
3	0.5	0.13583	3.2889	0.0328	29.6188	9.87
4	1	0.20013	4.8458	0.0484	43.6638	14.55
5	2	0.2877	6.9661	0.0696	62.7946	20.93
6	3	0.4709	11.401	0.1140	102.7867	34.26
7	4	0.68623	16.6158	0.1661	149.8257	49.94
8	5	0.8688	21.0379	0.2103	189.7909	63.26
9	6	1.0007	24.2316	0.2421	218.7446	72.91
10	7	1.0798	26.1460	0.2614	236.2169	78.74
11	8	1.13508	27.4837	0.2748	248.5176	82.84
12	9	1.1787	28.5407	0.2854	258.3053	86.10
13	10	1.2230	29.6142	0.2961	268.2517	89.42
14	11	1.2668	30.673	0.3067	278.0854	92.70
15	12	1.3024	31.5351	0.3153	286.1427	95.38

* All values are expressed as mean, n=3

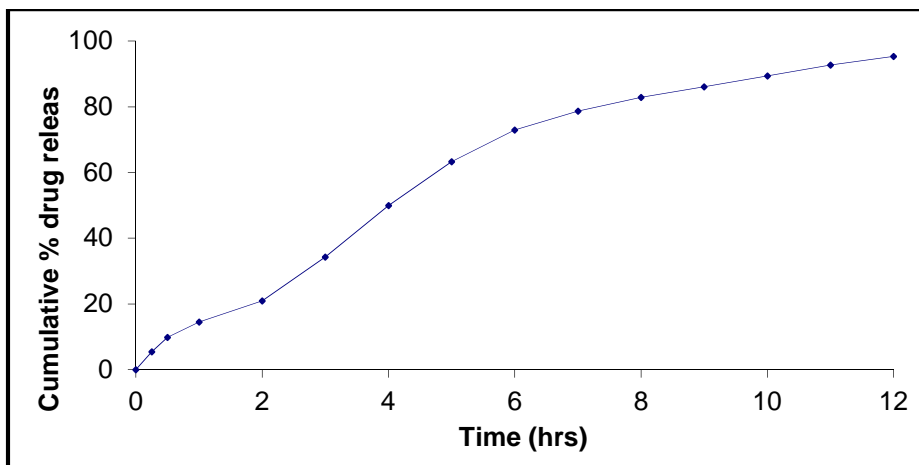


Figure No.1: *In-Vitro* release and kinetics profiles of formulation (F15)



Figure No.2: *In-Vitro* release and kinetics profiles of formulation (F15)

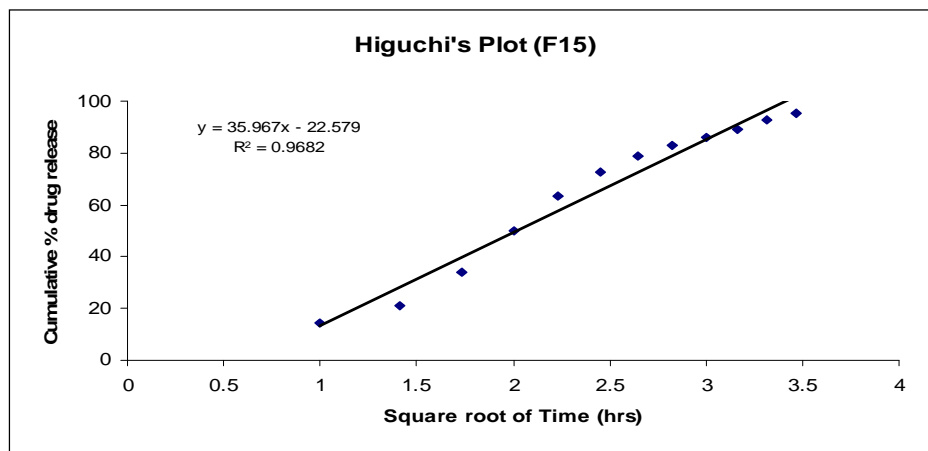


Figure No.3: *In-vitro* release and kinetics profiles of formulation (F15)

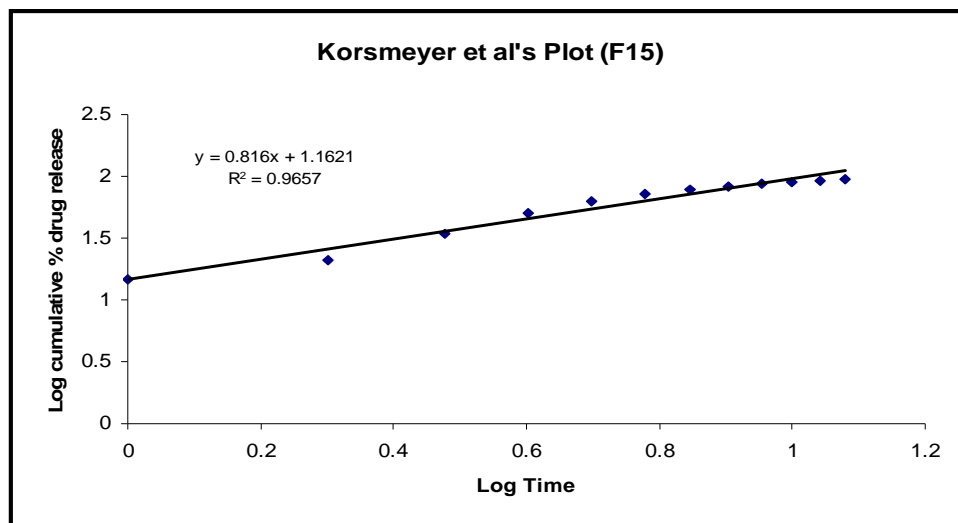


Figure No.4: *In-vitro* release and kinetics profiles of formulation (F15)

CONCLUSION

The hydrophilic matrix of HPMC alone could not control the diltiazem release effectively for 12 hours. It is evident from the results that a matrix tablet prepared with HPMC and a granulating agent of a hydrophobic polymer (EC, 4% wt/vol) is a better system for sustained release of a highly water-soluble drug like diltiazem.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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