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Original Article

DESIGN AND DEVELOPMENT OF TOPICAL HYDROGEL FORMULATION OF IRBISARTAN

ZEESHAN SHAIKH

Swami Vivekanand College of Pharmacy Indore, Madhya Pradesh, India
Email: jshaikh660@gmail.com

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ABSTRACT

Objective: Irbesartan is an antihypertensive with limited bioavailability. The objective of the study was to develop controlled release matrix tablets of irbisartan drug.

Methods: Tablets were prepared by wet granulation process. Result: *In vitro* drug release study revealed that HPMC causes initial burst release of drug hence combining HPMC sustained the action for 8 h (95.92±0.57% release). Fitting the *in vitro* drug release data to Korsmeyer equation indicated that diffusion along with erosion could be the mechanism for drug release. Compared to conventional tablets, the release of model drug from these HPMC matrix tablets was prolonged, leading to achieve an effective therapy with a low dosage of the drug, to reduce the frequency of medication. **T**he pharmacological and clinical properties of irbesartan, a noncompetitive angiotensin II receptor type 1 antagonist, successfully used for more than a decade in the treatment of essential hypertension.

Results: Compatibility Studies In order to investigate the possible interactions between irbesartan and distinct polymers and/or diluents, FT-IR and DSC studies were carried out. FT-IR results proved that the drug was found to be compatible with excipients as wave numbers are almost similar for pure drug and also drug excipients mixture. In picture 1 and 2. DSC studies indicate that chosen excipients for the formulation were found to be compatible with the active ingredient as the melting endothermic peaks are in the range of 250-320 °C which is same as the melting point of irbisartan.

Conclusion: Irbesartan exerts its antihypertensive effect through an inhibitory effect on the pressure response to angiotensin II. Irbesartan 150–300 mg once daily confers a lasting effect over 24 h, and its antihypertensive efficacy is further enhanced by the coadministration of hydrochlorothiazide.

Keywords: Irbisartan, Hydrogel, HPMC, Matrix tablet, Simplex lattice design and Oral controlled drug delivery system

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INTRODUCTION

Hydrogel the most promising alternative drug delivery systems for improving the bioavailability and therapeutic availability of the drugs. High patient compliance and flexibility in designing dosage forms attracted the oral drug delivery systems to be the most convenient mode of drug administration when compared to other dosage forms. Of these, matrix systems have gained widespread importance in controlled drug delivery due to cost-effective manufacturing technology [1, 2].

Matrix drug delivery systems are of two types: diffusion/swellable systems and dissolution systems. In diffusion systems, drug release is mainly governed by the hydration of matrices followed by diffusion of the drug molecules from the hydrated layer to the surrounding bulk solution, and sometimes, partially by erosion/dissolution. Cellulose ethers are the best examples of such systems. With dissolution systems, drug release is mainly due to dissolution/erosion of the matrix and hence, the achievement of constant drug delivery rate is easier by this systems1. Hydrophilic matrix tablets are among the most popular delivery systems for oral controlled release dosage forms. These hydrophilic matrices are widely accepted because of their biopharmaceutical and pharmacokinetics advantages over conventional dosage forms. This is largely because they offer exact modulation of drug release as a result of hydration of the constituent polymer(s), flexibility to obtain desired drug release profiles, cost-effectiveness, patient compliance, providing a constant, prolonged, and uniform therapeutic effect and broad Food and Drug Administration (FDA) acceptability. The swelling rate and erosion of HPMC-based matrix tablet in aqueous media are very crucial in terms of achieving the desired release profiles and are affected by parameters such as the physicochemical properties of the polymer and the drug, processing conditions, the testing medium used and the formulation composition. Hypertension is the leading cause of mortality in the world after malnutrition. Irbisartan is a competitive antagonist of Angiotension–II (AT II), devoid of partial agonistic activity and 10,000 more selective for AT1 and AT2 receptor, does not block any other receptor or iron channel. It blocks all over the action of AT II, the main adverse effect is dose-related hypotension. Irbisartan is a potent, highly specific angiotensin II type 1 (AT1) receptor antagonist with antihypertensive activity. It is readily absorbed from the gastrointestinal tract with oral bioavailability of about 33% and a plasma elimination half-life ranging from 1.5 to 2.5 h. Administration of LP in a controlled release dosage form with an extended release over 8 h, would be more desirable as these characteristics would allow a rapid onset followed by protracted anti-hypertensive effects by maintaining the plasma concentrations of the drug well above the therapeutic concentration. The current study aimed at developing and optimizing an oral sustained release dosage form of LP using computer-aided optimization technique i.e. simplex lattice statistical design with constraints on cumulative percentage release of drug after 8 h (95.92±0.57%). The Independent variables for the present study were: the amount of HPMC 15cps(C), amount of Ethylcellulose (D). The dependent variables studied were the 1 hour drug release(R1), 4 hr drug release(R2), 8 hr drug release(R3) and T50%-Time required for 50% drug release(R4)2 [1-6]

MATERIALS AND METHODS

Irbisartan was provided sun pharma dewas (m. p.). HPMC 15cps and Ethylcellulose, pvp, mg. stearate, aerosil and lactose.

Methods

Preparation of controlled release matrix tablets

The tablets were prepared by wet granulation method. The different stages involved in the process are: All the raw materials were passed

through sieve no. 60 and weighed accurately as per the formulae irbisartan, Polymers (HPMC 15cps and Ethylcellulose), PVP, Aerosil and Lactose were mixed thoroughly by triturating in mortar and pestle to get a uniform mix. The thoroughly mixed powder was kneaded for 10 min with Isopropyl alcohol solution till it forms dough mass. This mass was passed through sieve no. 20 to form granules. The granules were spread on the tray and kept for drying at 50 °C for 30 min using hot air oven. The dried granules were passed through the sieve no. 40 to get fines and uniform sized granules and blended with magnesium Stearate. The precompression parameters were studied. The controlled release matrix tablets were prepared using 8 mm biconcave round punch in 10 station rotary compression machine. The working formula is given in table 1 and 2.

Evaluation parameters

Evaluated for both precompression and post-compression parameters, they includes-Bulk density, Tapped density, Carr's Index, Angle of Repose, Hardness, Friability, Weight variation test, Thickness3 [4].

Drug content

Five tablets were powdered in a mortar. Weighed accurately the quantity equivalent to 50 mg of Losartan potassium and transferred to a 100 ml volumetric flask containing few ml of distilled water and mixed well, made up the volume up to 100 ml with distilled water. Pipette out 10 ml from the stock solution into another 100 ml volumetric flask and made up the volume with distilled water. From the above solution withdrew the aliquots of 2 ml, 2.4 ml and 3.2 ml (as per Beer's range 2-20 µg/ml) and the volume was made up to 10 ml with distilled water. The absorbance was measured at 262 nm using distilled water as blank.

***In vitro* release studies**

The *in vitro* dissolution profile of the designed formulations of controlled release tablets was carried out using USP type II apparatus under conditions specified (temp 37±0.50C, 75rpm). Tablets were subjected to dissolution for the first two hrs in 0.1 N HCl next six hrs till the end of dissolution studies. From the dissolution medium withdrawn and replaced 1 ml for every 5 min, for the solution withdrawn volume was made up to 10 ml with distilled water and absorbance was measured at 262 nm using distilled water as blank. Dissolution profiles of the formulations were analyzed by plotting drug release versus time plot.

RESULTS

Compatibility Studies In order to investigate the possible interactions between irbisartan and distinct polymers and/or diluents, FT-IR and DSC studies were carried out. FT-IR results proved that the drug was found to be compatible with excipients as wave numbers are almost similar for pure drug and also drug excipients mixture. In picture 1 and 2. DSC studies indicate that chosen excipients for the formulation were found to be compatible with the active ingredient as the melting endothermic peaks are in the range of 250-320 °C which is same as the melting point of irbisartan.

Evaluation of pre-compression parameters

Based on the results of pre-compression tests, all the formulations showed an angle of repose ranging from 22.21o±0.84 to 27.5o±0.94 indicating a good flow property (table 2) and Carr's index ranging from 10.53±0.01 to 23.22±0.22%, indicating compressibility of the granules is fairly passable (table 2).

Evaluation of post-compression parameters

The tablets of different formulations were subjected to various evaluation tests, such as thickness, uniformity of weight, hardness, friability, and drug content and the result are shown in table 3. All the formulations showed uniform thickness. The thickness and hardness of the tablets were in the range of 4.19±0.01 to 4.22±0.01 mm and 9.55±0.40 to 9.33±0.40 kg/cm2 respectively. The percentage friability was found to be less than 1% indicating that the friability is within the prescribed limits. In weight variation test, the average percentage deviation of all tablet formulations was found to be within the limit, and hence they met the test as per official requirements and were found to contain 40.32±0.66 to 54.17±0.47 mg of the labeled amount of irbisartan indicating uniformity of drug content.

In vitro release Tablets subjected for dissolution studies shown drug release at 1 hr was ranging between 17.58±2.97 to 32.52±0.30%. As the dissolution studies continued, the release from each dosage form showed an incremental release in sustained manner for a long time suggesting a Sustained-release pattern (fig. 1, 2 and 3). The release of the drug at 8 hr varied from 72.93±0.58 to 100.71±3.56 % indicating that the overall drug release from the dosage form depends upon the composition of tablet matrix which varies from one formula to another. From this study, it may be concluded, that the independent variables included in the study were found to show significant variation for the response variables.

Optimization

The optimized formulation (table 4) was prepared and evaluated for various precompression, post-compression parameters and various responses. Pre-compression parameters of optimized formulation having the Angle of repose in the range of 26.21 °±1.08 indicating a good flow property and Carr's Index in the range of 14.90±0.09 % indicating compressibility of the granules is passable (table 5). Post-compression parameters of optimized formulation having the weight variation in the range of 200.8±1.83 mg, thickness in the range of 4.20±0.01 mm, hardness in the range of 9.33±0.40 kg/cm2 and friability 0.07%, which shows all the post-compression parameters, met the test as per official requirements (table 6). In case of in-vitro dissolution profile, the optimized formulation showing drug release at 1 h was 18.87±0.72, at 4 h was 55.50±0.0 and release of the drug at 8 hr was 95.92±0.57 indicating that the overall drug release from the dosage form follows zero order drug release profile (fig. 3).

Stability studies

The optimized formulation was found to be stable in terms of physical appearance, hardness and drug content after 2 mo when it is stored under accelerated stability conditions as per ICH guidelines.

Table 1: Working Formula: F1–F5 by wet granulation method

S. No.	Formulation code	F1	F2	F3	F4	F5
1.	Drug	50	50	50	50	50
2.	HPMC 15caps	50	100	0	40	60
3.	Ethyle cellulose	50	0	100	60	40
4.	PVP	5	5	5	5	5
5.	Mg. stearate	4	4	4	4	4
6.	Aerosil	1	1	1	1	1
7.	Lactose	40	40	40	40	40
8.	Total wt.	200	200	200	200	200

The above quantites are expressed in terms of mg per tablet

Table 2: Pre-compression parameters of matrix tablets

S. No.	Formula	Bulk density	Tapped density	Carr's index	Angle of repose
1.	F1	0.46±0.00	0.53±0.00	14.16±0.03	26.79±1.15
2.	F2	0.41±0.00	0.49±0.00	18.54±0.03	27.86±0.22
3.	F3	0.47±0.00	0.52±0.00	10.54±0.01	22.86±0.22
4.	F4	0.47±0.00	0.56±0.00	10.54±0.01	22.88±1.08
5.	F5	0.38±0.00	0.56±0.00	14.85±0.04	26.80±1.09

Table 3: Post-compression parameters of matrix tablets

S. No.	Formula	Weight variation	Drug content	Hardness (kg/cm2)	Thickness (mm)	% fribility
1.	F1	200±1.02	40.32	9.55±0.40	4.19±0.02	0.10±0.00
2.	F2	199±1.32	38.52	10.11±0.32	4.19±0.01	0.15±0.01
3.	F3	201±1.22	36.82	8.5±0.52	4.19±0.01	0.25±0.10
4.	F4	200±0.01	41.32	9.33±0.22	4.19±0.01	0.51±0.00
5.	F5	201±1.2	54.17	8.66±0.36	4.19±0.01	0.17±0.02

Table 4: Optimized formula for matrix tablets

S. No.	Ingredients	Quantity per tab
1.	Irbisartan	50
2.	HPMC 15caps	60
3.	Ethyle cellulose	40
4.	PVP	5
5.	Mg. stearate	1
6.	Aerosil	4
7.	Lactose	40

Table 5: Pre-compression parameters of optimized matrix tablets

S. No.	Parameters	Result
1.	Bulk density(g/cc)	0.43±0.00
2.	Tapped density(g/cc)	0.50±0.00
3.	Carr's Index (%)	14.90±0.09
4.	Angle of repose(°)	26.21±1.08

Table 6: Post-compression parameters of Optimized matrix tablets

S. No.	Parameters	Result
1.	Weight variation(mg)	200.8±1.83
2.	Drug content(mg	52.68±0.72
3.	Hardness(kg/cm2)	9.33±0.40
4.	Thickness(mm)	4.20±0.01
5.	% Friability	0.07±0.00

Dissolution profile of formulation F1-F5

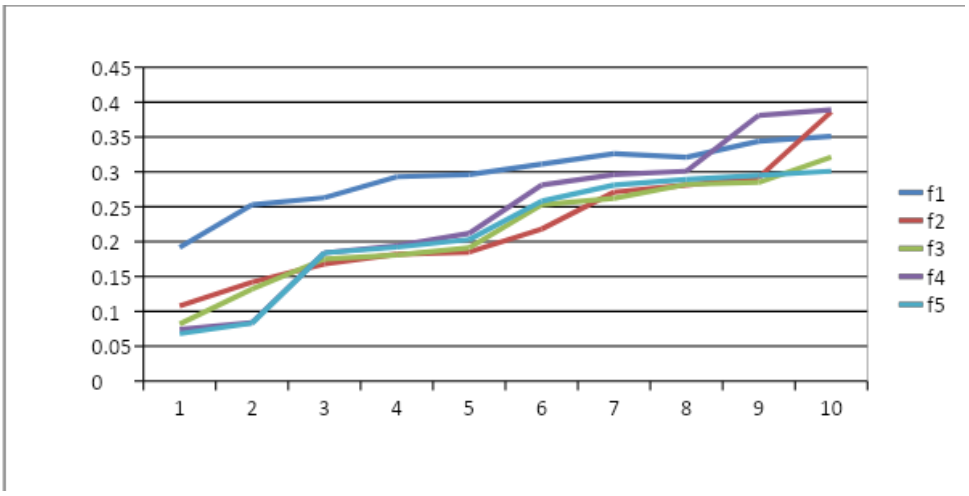
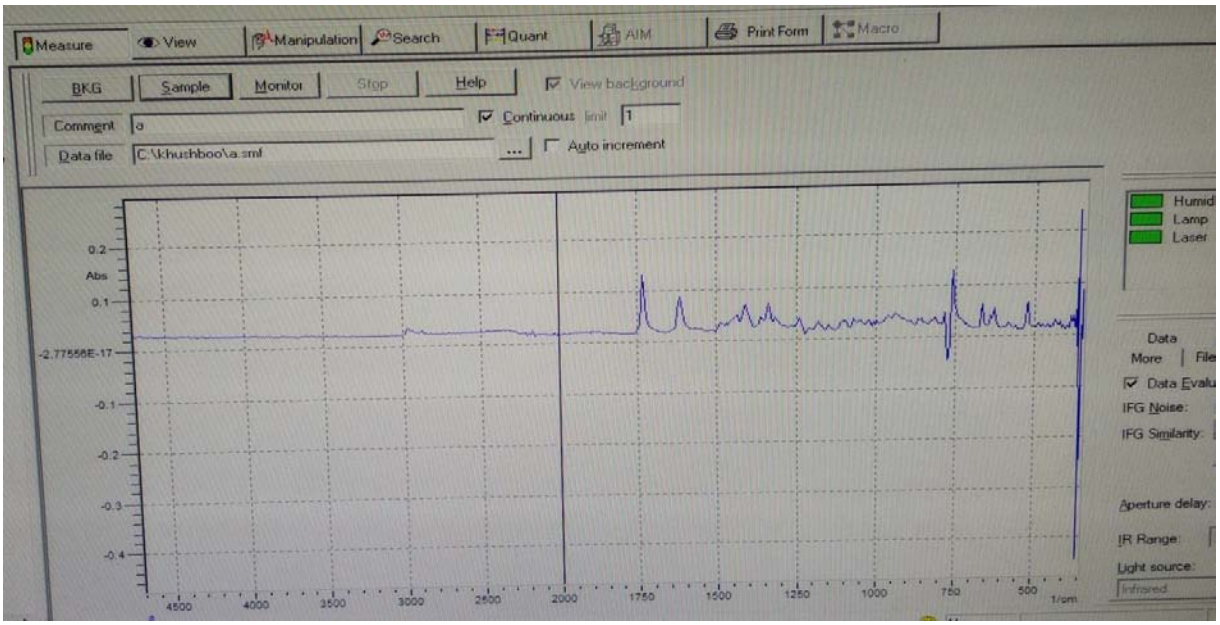
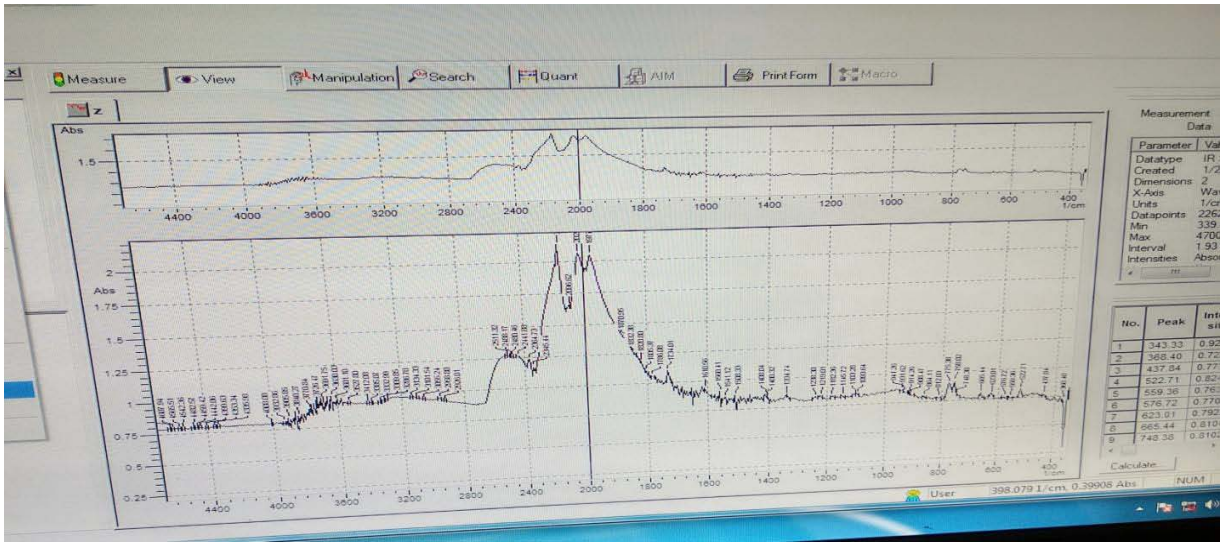


Fig. 1: Dissolution profile for matrix tablets of formulations F1–F5



Picture 1: Ft-Ir profile of irbisartan



Picture 2: Ft-Ir profile of irbisartan

CONCLUSION

The application of experimental design assisted in successfully developing an oral controlled release dosage form for irbesartan. Simplex Lattice design was used to study the effect of different formulation variables on the release profile to select optimized formulation by using a numerical optimization technique. Finally, it can be concluded that the preparation of a controlled release drug delivery system is simplified by the use of simple, cost-effective, naturally occurring excipients. This method may be promising in the field of preparation of delayed release dosage form as the drug release profile is complying with USP tolerance.

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AUTHOR CONTRIBUTION

All the work have been carried out by me

CONFLICT OF INTERESTS

Declare none

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