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Original Article

Formulation Variables Influencing Drug Release From Extended Release Formulation of Metformin Hydrochloride.

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Abstract

In the present research work study investigate the formulation variables influencing drug release of highly water soluble drug. Metformin Hydrochloride was selected as model drug for further research work. In the present work to study the effect of variables which are to be selected, how affects on drug release rate such as processing parameter (effect of method of preparation and effect of hardness) and Formulation parameters (effect of diluent and effect of polymer concentration). Method of preparation in which wet granulation and direct compression method are used. Effect of diluent in which three different types of diluents are used Lactose, Micro crystalline cellulose pH101 and Starch, and effect of polymer concentration in which vary the ratio of polymers on drug release rate. There are two types of polymers are used HPMC K-100M and Sodium carboxy methyl cellulose. For the in-vitro drug release study used USP Dissolution type II apparatus and pH 6.8 Phosphate buffer solutions is used as media in this investigation. Dissolution study is carrying out for 12 hrs. In last the optimized formulation fitting in the kinetic model (zero order, first order, Higuchi and Peppas) was carrying out the drug release mechanism.

Keywords: Metformin Hydrochloride, formulation Variables, Drug release.

Introduction

The prolonged release dosage forms have many advantages in safety and efficacy over immediate release products in that frequency of dosing can be reduced drug efficacy can be prolonged and the incidence of adverse effects can be decreased. Extended release drug formulations have been used since 1960's. These formulations make the drug available over an extended time period after oral administration. The extended release product will optimize the therapeutic effect and safety of a drug at the same time improving the patient convenience and compliance. By incorporating the dose for 24 hrs. Into one tablet from which the drug is slowly released. This formulation helps to avoid the side effects associated with low concentration and high concentrations.

The ideal drug delivery system should show a constant zero-order release rate and maintain the constant plasma concentrations. Metformin is used in the patients with type 2 diabetes; controlling high blood sugar helps prevent kidney damage, nerve problems, loss of limbs. The biological half life of Metformin HCL is 1.5-4.5hrs. Metformin extended release tablets reduces the dosage frequency and enhance the patient compliance. Dissolution is the process by which a solid of only fair solubility characteristics enters into solution. Dissolution rate may be defined as amount of drug substance that goes in the solution per unit time under standard conditions of liquid/solid interface, temperature and solvent composition. It can be considered as a specific type of certain heterogeneous reaction in which a mass transfer results as a net effect between escape and deposition of solute molecules at a solid surface. There are many factors which affects on dissolution rate of the

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drug. A) Factors related to Physico-chemical properties of drug which affects on dissolution rate are a) Drug solubility b) Particle size c) co-precipitation d) Salt formation and nature of powder like amorphous or crystalline. B) Factors related to manufacturing of dosage form like a) Method of preparation b) Compression force c) Mixing d) Milling e) Drug excipient interaction. C) Factors related to drug product formulation factor which affects on dissolution rate are a) Diluents b) Vehicles c) Granulating agent or Binder d) Disintegrant e) Lubricant f) coating components and Colorants. C) Factors relating dissolution apparatus which affects on dissolution rate a) Agitation b) Sterring element alignment c) Sampling probe position and filter D) Factors related to dissolution test parameter which affects on dissolution rate a) Temperature b) Dissolution medium c) Effect of pH) Volume of dissolution medium and sink condition e) Dearation of dissolution medium In this study, HPMC and Sodium CMC were used as extended release polymers. Here HPMC K 100M is hydrophilic polymer and sodium CMC also hydrophilic in nature.

Materials & Methods

Material:

All materials used in this study were of analytical grade Metformin HCL (Wockhardt Pharmaceutical pvt. Ltd, Aurangabad, India), HPMC-K100M (Balaji Drugs, Surat, India),Sodium CMC (Research-Lab Fine Chem. Industries, Mumbai, India), MCC pH-101 (Research-Lab Fine Chem. Industries, Mumbai, India), Lactose (Research-Lab Fine Chem. Industries, Mumbai, India) Starch (Research-Lab Fine Chem. Industries, Mumbai, India) PVP K-30 (Balaji Drugs, Surat, India), Isopropyl alcohol (Research-Lab Fine Chem. Industries, Mumbai, India), Magnesium stearate (Research-Lab Fine Chem. Industries, Mumbai, India), Aerosil (Research-Lab Fine Chem. Industries, Mumbai, India).

Preformulation study of drug:

To check out the identity, stability and purity of model drug. The characterization of the drug was carried out on the basis of standard official compendia methods such as melting point, assay and identification tests by using standard analytical technique such as Infrared spectroscopy, Differential scanning colorimeter and UV spectroscopy.

A) **Colour, odour, taste and appearance**.

B) **Melting point determination**
Melting point of Metformin HCL was determined by using Melting point apparatus (VEEGO Model-Vmp-0).

C) **Determination of solubility**
Soluble in water and pH 6.8 phosphate buffer.

D) **Assay**: Weigh accurately about 60mg dissolved in 4ml of anhydrous formic acid, add 50ml of acetic anhydride and titrate with 0.1N Perchloric acid carry out method A for non-aqueous titration determine end point potentiometricaly performed blank determination. Each ml of 0.1M Perchloric acid is equivalent to 0.008281gm of $C_4H_{11}N_5HCL$

E) **Infrared spectroscopy**
IR spectroscopy study of Metformin HCL was done by using FT-IR spectrophotometer (S). The spectra were scanned over the wavelength region of 400 cm^{-1}

F) **DSC**
Differential Scanning Calorimetric studies of pure Metformin HCL samples were carried out at the 10^0C/min between temperature range 30^0C-300^0C under a nitrogen flow of 2-bar pressure.

G) **UV Spectrophotometer**
UV spectrum of Metformin HCL solution in distilled water was scanned at 400 to 200 nm. The wavelength of maximum absorption (λ max) was determined

Preparation of calibration curve in Distilled water and Phosphate buffer 6.8.

A standard stock solution of Metformin HCL was prepared by dissolving accurate weighed 10 mg of Metformin HCL in small quantity of pH 6.8 phosphate buffer in 100 ml volumetric flask. The volume was then made up to 100 ml using water to obtain a stock solution of 100µg/ml. The absorbance of all these solutions was measured against a blank at 233 nm using UV spectrophotometer (Lab India 3000). A standard plot of absorbance v/s

concentration of the drug gives the standard calibration curve of Metformin HCL.

Evaluation of Tablet

Metformin HCL tablet were evaluated by using IPQC parameter such as thickness, hardness, weight variation, friability, weight variation, content uniformity and in-vitro drug release study.

Effect of variables on drug release

In the present study the effect of various variables on drug release such as effect on method of preparation, effect of diluents, effect of polymers and effect of hardness of Metformin HCL. In that study formulate the three batches of diluent (D1-D3), 3 batches of polymers (P1-P3), 2 batches of method of preparation (M1- Direct compression, M2- Wet granulation) and the 2 batches of hardness on randomly selected above formulation (P1, M2, D2). The composition of the above formulation is shown in the following table. All the formulation is evaluated by using IPQC parameter. The optimized formulations are optimized by using kinetic model such as zero order, first order, higuchi mode and Korsmeyer Peppas model.

Method of preparation

Direct compression method

Accurately weighted amounts of drug, Polymer and diluent were mixed geometrically in mortar. This mixture was passed through sieve no.40 mixed in polythene bag for 15 minutes. This powder blend was then lubricated with magnesium stearate and Aerosil for 2 minutes and compressed into tablets on a tableting machine**.**

Wet granulation method

Weighted Metformin HCL, MCC, Sodium carboxy methyl cellulose (of required grade) and HPMC K-100M were sifted using sieve no.60 and placed in separate poly bags. The sifted material were mixed for 5 minute and granulated with required quantity of binder by kneading method. The granules were passed through sieve and dried at an inlet temperature in tray dryer. Then the granules size reduced using sieve no.20. The granules finally lubricated using Magnesium stearate and Aerosil. The lubricated granules were compressed into tablet.

Results and Discussion

- Direct compression method involves compression of powders so powder showed high bulk density and low tapped density.
- Compressibility index of granules prepared by wet granulation technique was found to be below 15. Except formulation M1 so granules prepared by wet granulation have good flow property. Powder used to compress directly showed high compressibility index value and hence poor flow characteristics**.**
- Granules prepared by wet granulation showed Haussner's ratio less than 1.25 and hence they had very good flow property, poor flow properties indicated for powder compressed by direct compression**.**
- Granules prepared by wet granulation showed of all formulations angle of repose around or less than 30^0.so they had very good flow property. Powder compressed by direct compression had poor Flowability.
- Tablets of all formulations were within the acceptable range of weight and comply with Indian Pharmacopoeial specifications for weight variation.
- Tablets of all formulation were not friable and content uniformity was also in acceptable range and complies with Indian Pharmacopoeial specifications.
- The hardness of all tablets was in the range of 9 to 11kg/cm^2
- M1 and M2 were formulations were used to prepare tablets by two different methods direct compression and Wet granulation respectively.
- Each method has different release profile of drug. Release rate was increased in order of direct compression and Wet granulation respectively.
- In the direct compression method in which the drug is released 98.35% in 9hrs, but in wet granulation technique the drug released slowly upto the 12 hrs (99.45).
- So in above study we conclude that the wet granulation method the tablet

is swelled slowly as compare to direct compression method.

- Drug release rate was very slow with tablets prepared MCC pH101 and drug release rate was very fast with tablets prepared by starch as a diluent.
- Lactose released highest amount of drug in 9hrs because of it's highly solubility nature in water.
- High solubility of lactose caused the formation of pores in large number resulting in highest release.
- Tablets containing lactose and tablets containing MCC pH101were intact throughout the dissolution study.
- Disintegration of tablets containing MCC pH101 may be due to absorption of dissolution media leading to swelling and then disintegration.
- Starch tablets disintegrated after four hours resulting in release of more drugs. This was due to absorption of dissolution medium and swelling of tablets.
- The sustaining effect of drug release decreased in order, lactose, starch and MCC respectively with polymers concentration.
- These investigations suggest that MCC pH101 is the best diluent for matrix tablets.
- P1 to P3 formulations are prepared with different concentration of polymer i.e. HPMC K-100M and sodium carboxy methyl cellulose are used as polymer.
- In these formulations HPMC K100M & Sodium CMC (release retardant polymer) is used in the formulation P1-P3 in different concentration for the study of release of drug through swellable matrix for a period of 12 h.
- They are non toxic, hydrophilic in nature and also having adequate swelling properties that allows rapid formation of gel layer which retards or play a major role in controlling drug release.
- In these formulations from P1-P3 in which P2 formulation is release highest amount of drug 91.56% and P3 formulation s release low amount of drug 89.58 upto 12 h.
- In above three formulations P1-P3, in which the P2 is better formulation because the P2 formulation shows good drug release kinetics 91.56% upto 12h compare to other two formulation.
- In these formulations large amount of polymer is present due to swelling of tablet and formation of gel layer it will be fast within 0.5 hr.
- Formulations P1, M2 and D2 were used to prepare tablets of hardness 4.0, 8.0 and 10 Kg/cm^2 respectively.
- As the hardness of the tablets was increased from 4.0 Kg/cm^2 to 10 Kg/cm^2, the drug release rate was decreased.
- Desired drug release profile was obtained with tablets having hardness 10 kg/cm^2.
- As the hardness is increased the drug release rate was decreased due to decrease in the interparticle spaces and intergranular spaces.

Conclusion

The aim of the present study of variables influencing drug release from the extended release matrix tablet of Metformin HCL using hydrophilic polymers like HPMC K100M & Sodium CMC. In the present research work to study of various factors how it can be affect the drug release such as processing factor (Method of preparation and Hardness) and formulation factor (Effect of diluent and concentration of polymers). In the present research work effect of diluent on drug release use of diluent (Lactose, Microcrystalline cellulose Ph101 and Starch).

The effect of diluent in-vitro drug release concluded that MCC pH101 is better diluent for preparation of ER of Metformin HCL. In which used other two diluents lactose and starch does not shows drug release upto 12h, because lactose is highly water soluble diluent. In these study the effect of method on preparation is also affect on the drug release kinetics, in which the ER tablet prepare by both direct compression and wet granulation. In that direct compression method does not

shows the drug release kinetics upto 12h, so the wet granulation method is better for ER tablet formulation. The effect of hardness on ER formulation is also major variables in drug release kinetics.

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Table 1. Characterization & UV absorbance of Metformin HCL.

Sr. No	Test	Specification	Test Result
1	Description	White crystalline powder	White crystalline powder
2	Melting point	222-226^{0}C	223-225^{0}C
3	Assay	99.99%	99.5%

Sr. No	Concentration (ppm)	Absorbance (233nm)
1	5	0.640
2	10	0.707
3	15	1.084
4	20	1.412
5	25	1.928

Table 2A. Composition of batch M1-M2.

Sr. No	Ingredients	M1	M2
1	Metformin HCl	500	500
2	HPMC K100M	150	150
3	Sodium CMC	50	50
4	MCC- pH 101	200	200
5	PVP-K30	40	40
6	Isopropyl alcohol	-	q.s
7	Magnesium stearate	1%	1%
8	Aerosil	1%	1%

(M1-Direct compression, M2- Wet granulation)

Table 2B. Composition of diluents (D1-D3).

Sr. No	Ingredients	D1	D2	D3
1	Metformin HCl	500	500	500
2	HPMC K100M	150	150	150
3	Sodium CMC	50	50	50
4	Lactose	100	-	-
5	MCC- pH 101	-	100	-
6	Starch	-	-	100
7	PVP-K30	40	40	40
8	Isopropyl alcohol	q.s	q.s	q.s
9	Magnesium stearate	1%	1%	1%
10	Aerosil	1%	1%	1%

(D1-Lacctose, D2- MCC- pH 101, D3- Starch)

Table 3. Composition of polymers (P1-P3).

Sr. No	Ingredients	P1	P2	P3
1	Metformin HCl	500	500	500
2	HPMC K100M	200	220	210
3	Sodium CMC	50	30	40
4	MCC- pH 101	100	100	100
5	PVP-K30	40	40	40
6	Isopropyl alcohol	q.s	q.s	q.s
7	Magnesium stearate	1%	1%	1%
8	Aerosil	1%	1%	1%

Each formulation contains 1% Magnesium Stearate, 1% Aerosil of total weight.

Table 4. Effect of Hardness.

Sr. No	1	2	3
Batch No.	P1	M2	D2
Hardness (kg/cm^2)	4	8	10

Table 5. Precompression parameter of Matrix tablet.

Formulation code	Bulk density (gm/ml)	Tapped density (gm/ml)	Compressibility index (%)	Haussner's ratio	Angle of repose (ϴ)
M1	0.899	0.687	20.58	1.29	42.66
M2	0.512	0.632	13.47	1.15	15.46
D1	0.719	0.854	15.80	1.18	25.02
D2	0.529	0.665	14.45	1.15	27.54
D3	0.699	0.776	9.92	1.11	20.0
P1	0.656	0.722	12.78	1.14	22.57
P2	0.621	0.744	15.53	1.19	23.48
P3	0.658	0.734	10.34	1.11	21.54

Table 6. Post-compression parameter of Matrix tablet.

Formulation code	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Weight variation	Drug content (%)
M1	6.9	10	0.244	Pass	98.86
M2	6.8	11	0.252	Pass	99.31
D1	6.7	9.5	0.533	Pass	97.69
D2	6.0	10.5	0.202	Pass	98.49
D3	6.6	9.2	0.611	Pass	98.08
P1	6.8	9.0	0.283	Pass	97.14
P2	6.6	10	0.246	Pass	98.26
P3	6.8	11	0.711	Pass	99.52

Table 7. Cumulative % Drug Release.

Time (hr)	Cumulative % release (Mean±S.D)							
	M1	M2	D1	D2	D3	P1	P2	P3
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	45.02±1.15	35.76±1.15	46.97±1.15	28.37±1.56	47.25±1.15	24.50±0.75	27.41±0.15	28.29±0.75
2	61.312±1.89	48.76±0.05	54.29±0.44	37.65±0.15	59.09±1.50	33.24±1.75	34.11±0.44	36.43±0.86
3	71.93±1.49	59.07±0.07	65.11±1.57	42.86±0.47	71.99±0.75	40.27±1.57	41.61±1.15	42.15±0.75
4	80.85±0.76	66.85±0.89	72.09±1.11	49.85±1.16	88.99±1.15	45.11±1.17	48.79±1.11	49.22±1.15
5	86.06±0.05	75.026±0.76	82.72±1.30	59.41±1.32	91.70±0.75	52.24±0.77	55.56±0.74	54.79±0.76
6	89.53±0.10	81.50±1.14	90.72±0.44	65.50±1.33	98.72±0.44	58.08±0.78	61.55±1.11	60.40±0.44
7	93.06±0.75	87.05±0.04	94.96±0.46	71.36±0.41	-	67.04±1.17	68.88±0.54	65.54±0.77
8	96.04±0.04	91.18±1.14	97.98±0.76	78.31±0.39	-	73.02±0.42	74.72±0.34	69.45±0.77
9	98.35±0.02	93.68±0.75	99.11±0.74	84.32±0.41	-	78.27±0.40	79.54±0.06	74.88±0.73
10	-	95.98±0.75	-	88.03±0.75	-	81.03±0.44	85.19±0.55	79.85±0.42
11	-	97.91±0.45	-	91.50±0.75	-	86.30±0.47	88.13±0.10	84.83±0.42
12	-	99.45±0.04	-	98.76±0.45	-	90.56±0.49	91.78±1.10	89.58±0.43

Table 8. Cumulative % Drug Release.

Time (hr)	Cumulative % drug release (Mean±S.D)		
	P1(4 kg/cm^2)	M2(8kg/cm^2)	D2(10 kg/cm^2)
0	0.00	0.00	0.00
1	45.30±0.25	25.60±0.13	40.26±1.13
2	52.50±016	36.52±1.29	49.75±0.75
3	66.31±0.13	48.32±0.51	56.26±1.16

4	79.41±1.14	56.22±0.44	62.40±0.88
5	87.32±0.12	65.38±0.88	69.25±1.52
6	96.47±0.15	77.14±0.65	76.46±1.58
7	-	83.41±0.78	80.47±0.13
8	-	89.25±31	84.29±0.45
9	-	96.22±0.63	89.27±0.15
10	-	-	92.90±1.59
11	-	-	95.24±0.78
12	-	-	97.66±0.64

Table 9. Release kinetics of formulations.

Sr No	Batch code	Zero order kinetics	First order kinetics	Higuchi Model	Peppas Model
1	M1	0.859	0.977	0.974	0.973
2	M2	0.840	0.979	0.981	0.988
3	D1	0.840	0.945	0.980	0.979
4	D2	0.933	0.823	0.993	0992
5	D3	0.872	0.913	0.990	0.981
6	P1	0.947	0.973	0.990	0.987
7	P2	0.969	0.974	0.997	0.998
8	P3	0.933	0.966	0.996	0.990

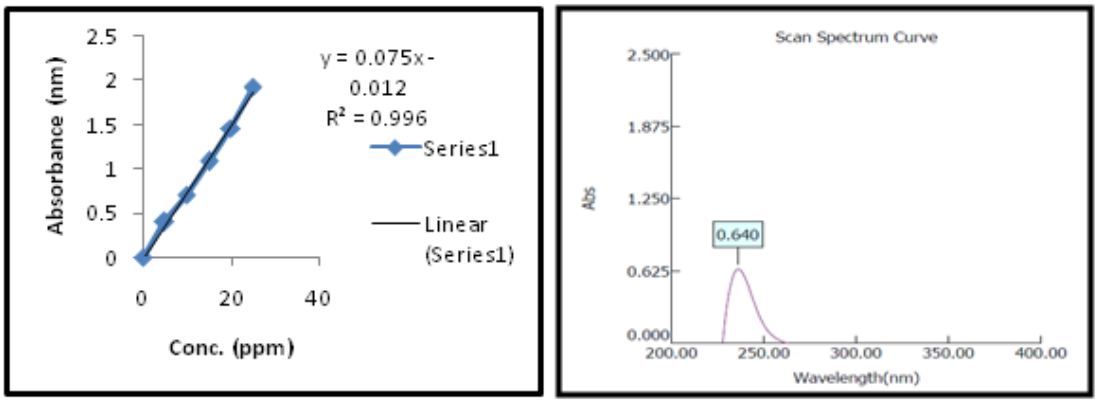

Fig. 1. Calibration curve & λ max of Metformin HCL.

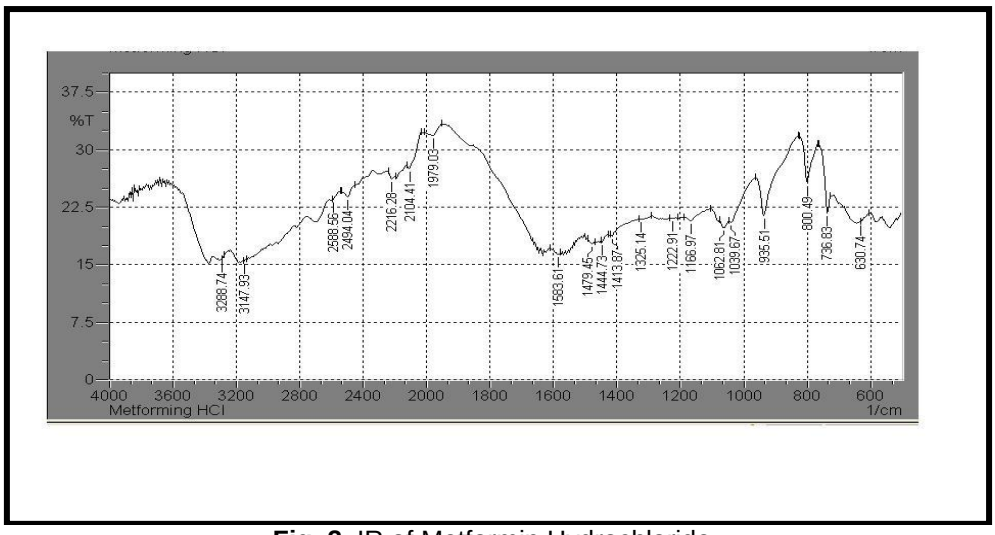

Fig. 2. IR of Metformin Hydrochloride.

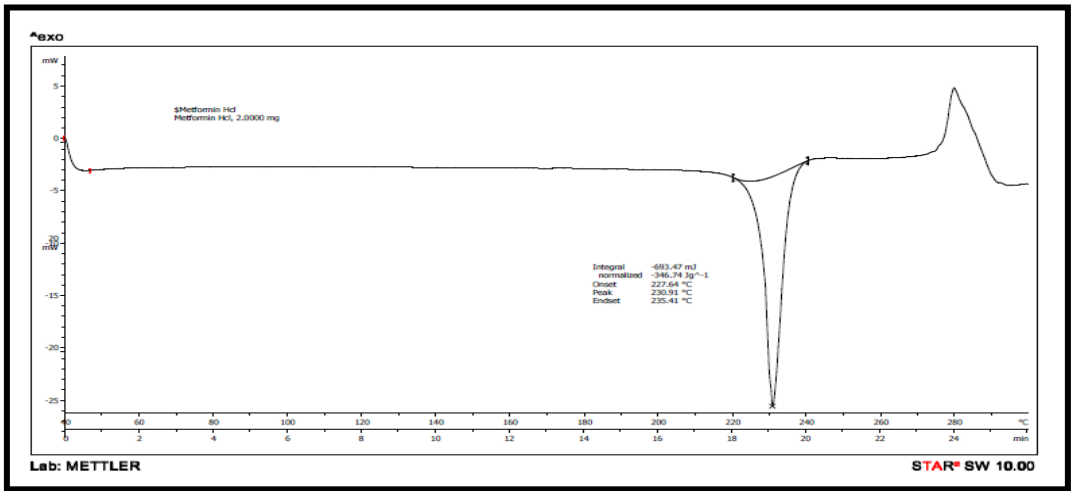

Fig. 3. DSC of Metformin HCL.

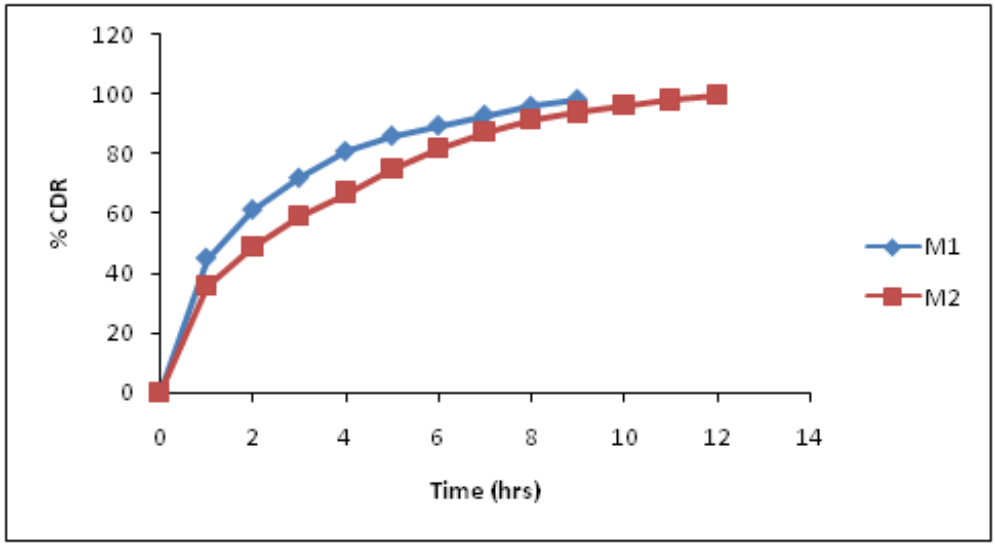

Fig. 4. *In-vitro* Drug Release Profile of M1-M2.

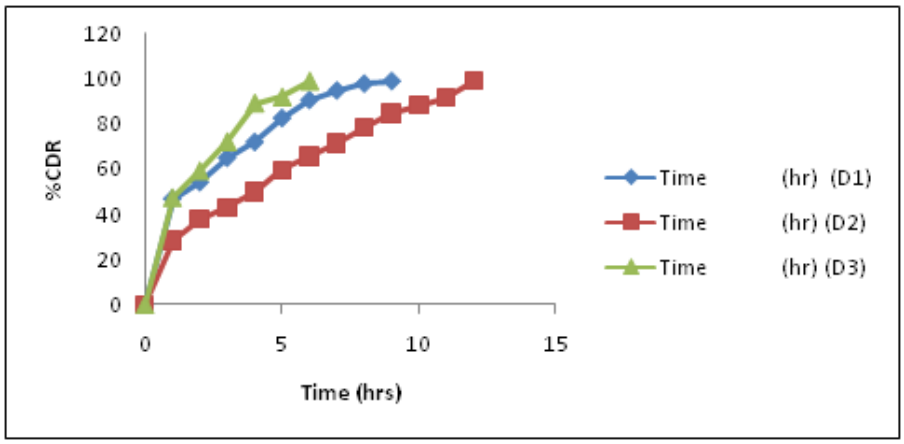

Fig. 5. *In-vitro* Drug Release Profile of Diluent D1-D3.

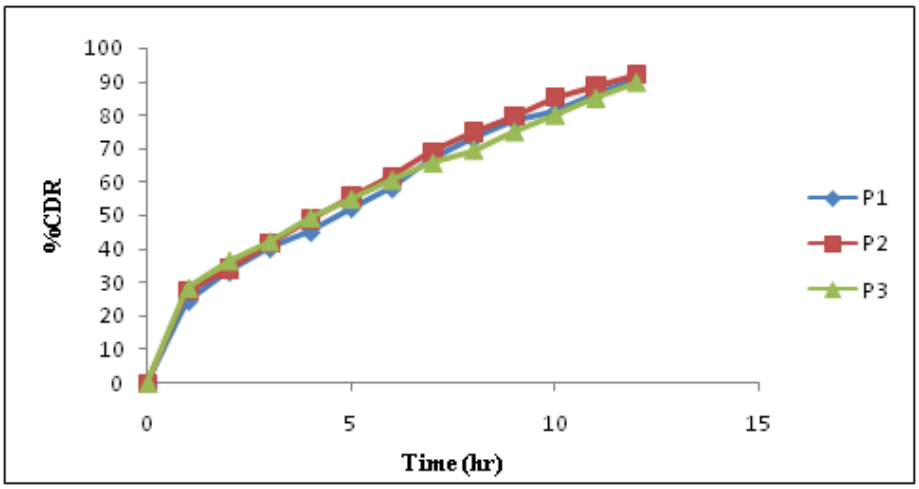

Fig. 6. *In-vitro* Drug Release Profile of P1-P3.

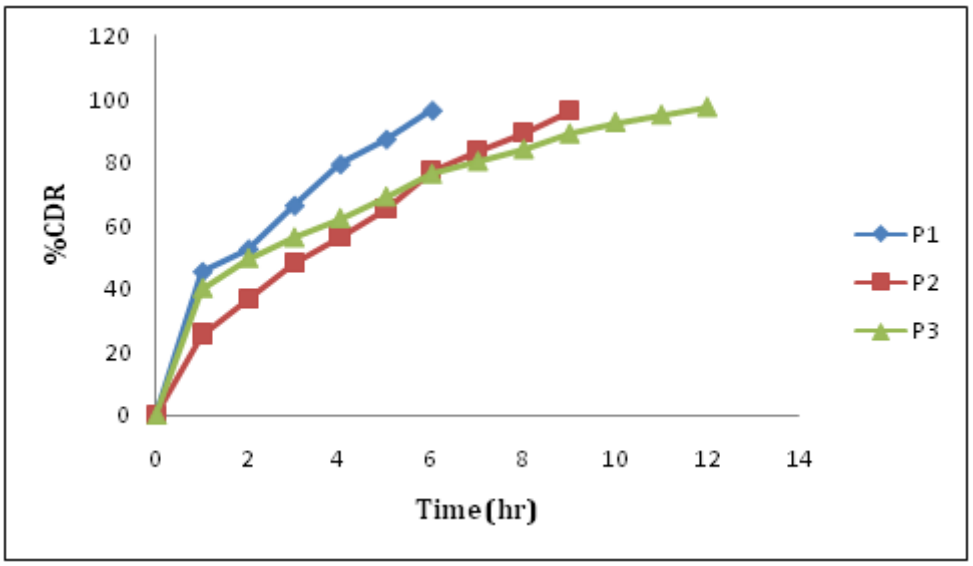

Fig. 7. Effect of Hardness on drug release in pH phosphate buffer 6.8.

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