FORMULATION, CHARACTERIZATION AND RELEASE BEHAVIOUR OF METFORMIN HYDROCHLORIDE MODIFIED RELEASE TABLET BY USING HYDROPHILIC POLYMERS

Abstract

Amongst the many public health problems, the diabetes mellitus is considered as a chronic life-style related disease which is now growing as an epidemic in both developed as well as developing countries. The current study is about formulation of metformin hydrochloride tablet to confirm their sustained release property by using various polymers. The tablets are prepared by granulation techniques using binding solution containing polyvinyl pyrolline K30. The possible interaction between the pure metformin hydrochloride and polymers are identified by Fourier transform-infrared spectroscopy. Tablets were formulated with different polymers like Hydroxy propyl methyl cellulose K100 and sodium carboxymethyl cellulose. Matrix prepared with high concentration of HPMC K100 polymer retards the drug release up to 6 h at 59 %, but the formulation 3 (F3) showed 72.72% of drug release in 6 h. The release of drug from the F3 formulation was found to be prolonged drug release when compared to other formulations. Hence our study conclude that the HPMC K100 polymer containing formulation showed good sustained release property owing to the high gel strength and well high viscosity nature of the polymer.

*Keywords**:** Metformin hydrochloride, HPMC K 100, PVP K 30, CMC, sustained release tablet*

1.INTRODUCTION

Diabetes mellitus is a chronic disease suffered by approximately 150 million people out of which 35 million people are Indians. The available antidiabetic drugs are used to treat diabetes mellitus and insulin resistance. The antidiabetic drugs are classified as biguanides, thiazolidinediones, the sulfonyl ureas, benzoic acid derivatives and alpha glucosidase inhibitors. The biguanide drug, metformin is currently prescribed by most of the physicians worldwide. An ideal drug delivery formulation should release required amount of drug inside human body to desired therapeutic effect. Nowadays, sustained release dosage formulations are main focus of the pharmaceutical research field to avoid noncompliance by the patient and to reduce adverse drug reactions. The novel sustained release dosage form should be able to

maintain drug concentration in blood and tissue for extended or sustained period of time. The ideal SR dosage form is obtained by trying "zero order" release dosage form without the influence of the delivery system [1-4].

The oral antidiabetic drugs are formulated as tablets and capsules. Those tablets and capsules are modified into controlled drug delivery formulation and sustained drug delivery formulation. Matrix tablets are widely acknowledged for oral controlled release tablet, as they are easy to formulate. The controlled release dosage forms are formulated using polymers and release-retarding materials as matrix. The rate of drug released from ideal oral sustained release formulations is based on the polymer concentration. The intrinsic properties of the drug or the situation of GI tract should not affect the formulation. The drug molecules exhibited higher permeability across the gastrointestinal epithelium. The absorption rate of the drug is controlled by the rate of drug released from the formulation [5-9].

Our present study focused to formulate the metformin hydrochloride tablet to confirm their sustained release property by using various polymers such as, Hydroxy propyl methyl cellulose K100 and sodium carboxymethyl cellulose based on their high gel strength and viscosity properties.

2.METHODOLOGY

Metformin drug was purchased from Himedia lab pvt ltd., Mumbai and HPMC K 100 was purchased from phoenix Pharma, Pondicherry. Lactose, PVP K30, talc, aerosil, sodium hydroxide and sodium CMC were generous gift sample from Nice chemicals, Cochin, Kerala. Magnesium stearate was get from loba chemicals, Mumbai. UV Spectrophotometer, FT-IR, Type II Dissolution apparatus, tablet compression machine.

Parameters for preformulation:

Precompression study parameter of the pre-formulation was determined to find out the flow and compression properties of granules before compressing into tablet form Bulk density, tapped density, angle of repose, compressible index, Hausner ratio.

Bulk Density

The 25 gram of the drug is weighed after passing through sieve (no. 20). The drug was then transferred into a graduated cylinder (100 ml). The powder is carefully leveled without compaction and apparent volume (Vo) is measured. The apparent bulk density (gram per ml) is calculated by dividing powder weight by bulk volume [4].

Tapped Density:

Metformin hydrochloride (25 gm) is weighed after passing through the sieve (no. 20) and transferred into graduated cylinder (100 ml). The cylinder is then tapped mechanically using density tester

and the drug is allowed to settle. The tester provided a fixed drop of 14 ± 2 mm at a rate of 300 drop per minute. Again, the cylinder is tapped for 500 and 750 times, respectively and initial volumes (V, V_1) were measured [10, 11]. If the difference between the volumes (V and V_1) was less than 2 %, then the obtained volume was considered as final volume (V_2). The final tapped density (gram per ml) was determined by dividing weight of the powder by final tapped volume [4]

Angle of Repose:

The angle of repose (θ) is measured by fixed funnel method by adjusting the height of the funnel in order to touch the apex of the granular heap. The prepared granules flowed freely through the funnel and the angle of repose is calculated by using the below formula.

$$\theta = \tan^{-1}\left(\frac{h}{r}\right) \text{ [4]}$$

Where, h is the height of the granular heap and r is the radius of the granular circle.

Compressible Index (Carr's Index):

Carr's Index is a parameter to measure the flow properties of the powder and it is measured using below equation

$$I = (D_t - D_b / D_t) \times 100$$

Where, D_t is the tapped density of the powder and D_b is the bulk density of the powder [4].

Hausner Ratio:

Hausner ratio is the flowability of a powder or granular material measured by the below given formula.

$$\text{Hausner ratio} = D_t / D_b$$

Drug excipients compatibility studies

The drug-excipient compatibility is determined using FT-IR. The drug and excipients are mixed with KBr pellets and scanned at a speed of 400-4000 cm^{-1} [12-16]. The peak values, spectra and the functional groups of the mixture are compared with standard values.

Fabrication of Sustained Release tablet containing Metformin:

The sustained release formulation of metformin was prepared by wet granulation method by mixing with various ingredients and various batches listed in the table 1.

All the ingredients were thoroughly blended with addition of PVP K 30 solution and then magnesium stearate and talc were added. The blend is compressed into tablets with 16/32 flat punches by

keeping average weight of 700 mg. The variation in weight, tablet hardness, tablet thickness, tablet friability and dissolution rate of the compressed tablet were evaluated [17-20].

TABLE 1: Formulation of Metformin hydrochloride Sustained Release Tablets

INGREDIENTS	F_1	F_2	F_3	F_4	F_5	F_6	F_7
Metformin	500 mg	500 mg	500 mg	500 mg	500 mg	500 mg	500 mg
HPMC K100	120 mg	115 mg	-	-	-	-	-
Sodium CMC	-	-	105 mg	110 mg	115 mg	120 mg	125 mg
Lactose	42 mg	42 mg	42 mg	42 mg	42 mg	42 mg	42 mg
PVP K30	15 mg	20 mg	30 mg	35 mg	40 mg	45 mg	50 mg
Magnesium Stearate	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg
Talc	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg
Aerosil	3 mg	3 mg	3 mg	3 mg	3 mg	3 mg	3 mg
Distilled Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s

In vitro Dissolution Studies

The *in-vitro* drug release profile of the prepared sustained release tablet is measured using USP type II dissolution apparatus. The phosphate buffer was filled in the basket of apparatus as the dissolution medium at 37 ± 0.5 ^{o}C for 6 hours[17-18] For every one hour intervals, sample (5 ml) was withdrawn from the dissolution medium and replaced with fresh buffer solution to maintain constant volume. After filtration, dissolution was measured using UV spectrophotometer.

Properties of optimized sustained release tablets

The compressed tablets are checked for quality control parameters (weight variation, thickness, hardness, friability, drug content, and in-vitro drug release behavior).

Hardness

The hardness of the tablet is measured by tablet crushing load using the tablet hardness tester (Pfizer hardness tester). The tablet crushing load is the load required to break the tablet.

Weight variation test

Tablets are randomly selected from each formulations and weighed separately. The average weight of tablet is determined from the measured values.

Friability

The friability of the tablets were measured using Roche friabilator™ at 100 rpm. The tablets are weighed again and percentage friability was calculated using the below formula.

$$Percentage\ Friability = initial\ weight - Final\ weight \div initial\ weight \times 100$$

Estimation of Amount of Drug

Tablets (10) from each formulation are powdered. The phosphate buffer (pH 6.8) was used to dissolve the powdered tablets. The diluted solution was analyzed by UV and DBSM at 233 nm [21-23].

Thickness

Size and thickness of the tablet were measured using screw gauge. The thickness of tablet obtained was related to tablet hardness.

Drug Release Kinetic Profile

The release kinetics of the tablet at zero order and first order were measured using Higuchi and Korsmeyer-peppas model [23-25].

3.RESULTS

Pre-formulation Studies

Properties of compressed granules

The properties of granules before compression are given in table 2. The obtained result indicated that the flow properties of powder was better for smooth tablet compression.

TABLE 2: Pre-compression Parameters

Formulations	Bulk density (g/ml)	Tapped density (g/cm^3)	Compressibility	Hausner Ratio	Angle of Repose
F_1	0.53	0.62	12.35	1.14	22.5
F_2	0.51	0.60	13.40	1.13	24.7

F_3	0.57	0.65	12.48	1.06	25.9
F_4	0.54	0.62	13.40	1.13	24.6
F_5	0.49	0.60	12.42	1.11	22.6
F_6	0.47	0.61	12.56	1.10	23.6
F_7	0.45	0.63	13.20	1.09	21.6

Compatibility Studies

The FT-IR spectra of metformin HCl, HPMC K100, sodium CMC and their composition was measured. It is shown that a high intense stretching frequency occurring at 3371.34 and 1625.88 cm^{-1} correspond to –OH and $–NH3^+$ groups is present in metformin HCl. CH showed 1475.44 cm^{-1} corresponding to NH_3+ groups, HPMC K100 showed peak at 3445.56 cm^{-1} assigning to –OH groups, and sodium CMC showed 3419.56 cm^{-1} corresponding to –OH groups. In case of drug and polymer composition, the broadening of bonds appeared at ranges of 3523.70, 3371.34, 3294.19 cm^{-1}, respectively. This can be inferred due to intermolecular hydrogen bonding between drug and polymers. The result concluded that there was no chemical interaction between drug and polymers, shows the formulated tablet (F3) more stable (Figs:1-4).

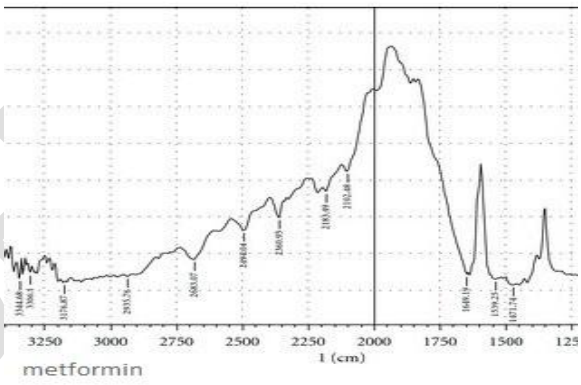

Fig:1 FTIR of metformin

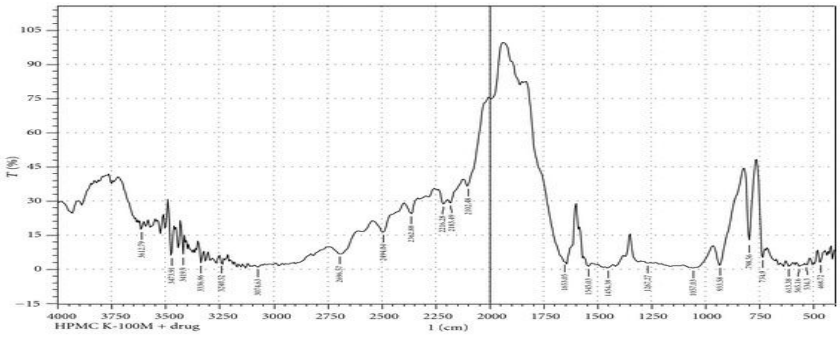

Fig:2 FTIR of metformin +HPMC K100

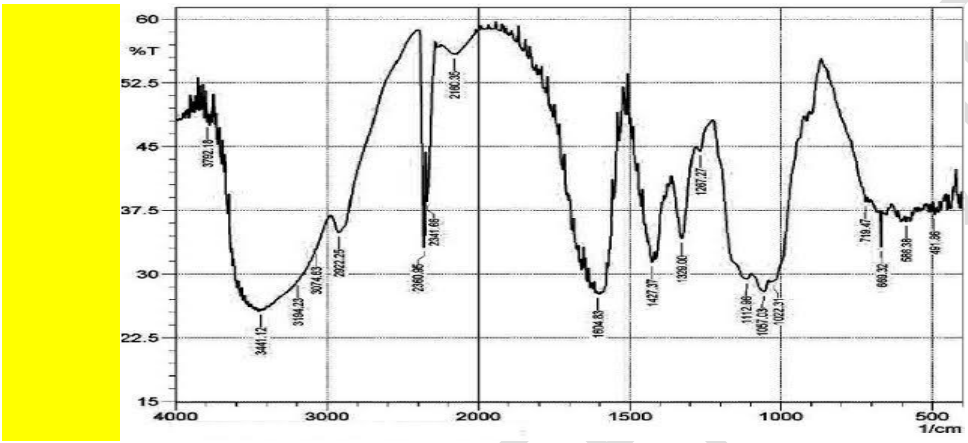

Fig:3 FTIR of formulation 3

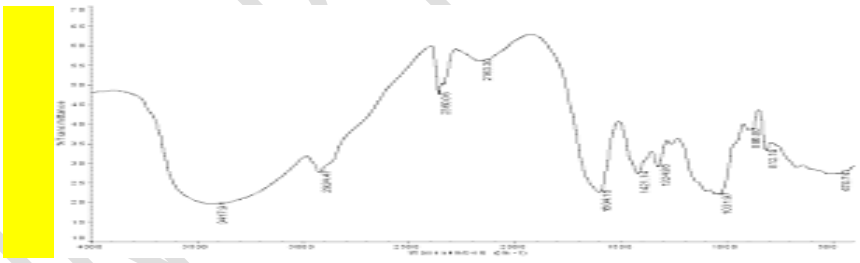

Fig :4 metformin+sodium cmc FTIR

Post Compression Parameters:

The results of parameters of compressed tablets are illustrated in table 3.

Table 3: The results of parameters of compressed tablets are illustrated

Formulation	Weight Variation (%)	Hardness (Kg/cm^2)	Thickness (mm)	Friability (%)
F_1	710 ± 10	4.34 ± 0.35	4.96 ± 0.03	0.547 ± 0.27
F_2	700 ± 10	4.81 ± 0.12	4.98 ± 0.02	0.57 ± 0.19
F_3	720 ± 10	3.79 ± 0.52	4.97 ± 0.02	0.273 ± 0.35
F_4	710 ± 10	3.81 ± 0.47	5.01 ± 0.01	0.731 ± 0.11
F_5	700 ± 10	4.45 ± 0.51	5.22 ± 0.05	0.621 ± 0.12
F_6	705 ± 10	5.66 ± 0.40	5.25 ± 0.03	0.581 ± 0.18
F_7	710 ± 10	6.70 ± 0.42	5.38 ± 0.01	0.430 ± 0.19

***In-vitro* Dissolution Profile**

In-vitro release data from controlled release formulation were carried out for six hours and graphically represented as percentage drug release verses time profile. Dissolution rate of pure metformin is very low. Only 27.64% of the drug was released in phosphate buffer at the time end of six hours. The sustained release of drug from the formulation rate is increased more than the pure drug, due to the increase in surface of the drug and possible better contact with polymer between the formulations and dissolution medium.

The results of dissolution studies indicated that F_1-F_7 released 56.89%, 59.28%, 72.72%, 63.25%, 56.25%, 51.56% & 54.98% of drugs, respectively. Dissolution studies prove that our modified tablet formulation F3 have shown 72.72% of drug in six hours. The result showed that considerable amount of drug was released for a period of up to six hours. Minimum amount of drug released within two hours in phosphate buffer (pH 6.8). The release of formulation F3 was prolonged than the other formulation showing the fig.no.1.

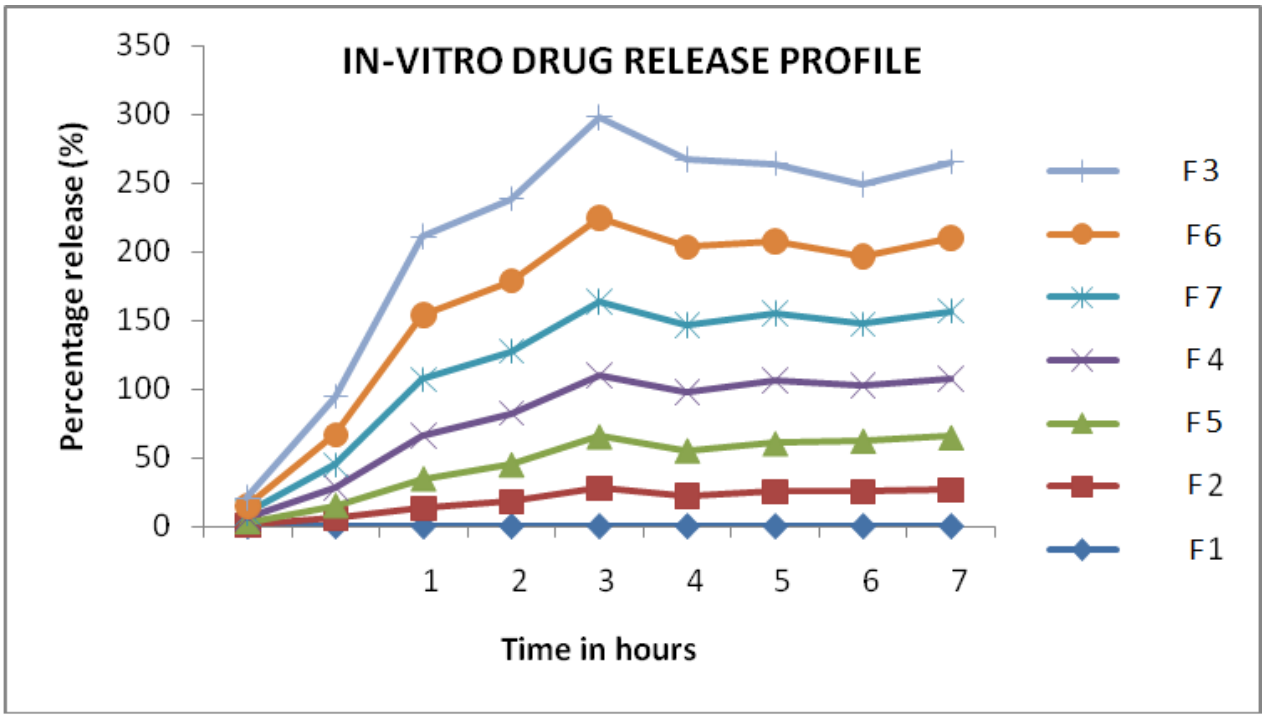

Figure 5: *In-vitro* drug release profile

Drug Release Kinetic Profile

The kinetic data of the drug formulation was checked in zero order, first order, Higuchi and Korsemeyer and peppas model, respectively. The results were showed in the histogram graph figure 2.

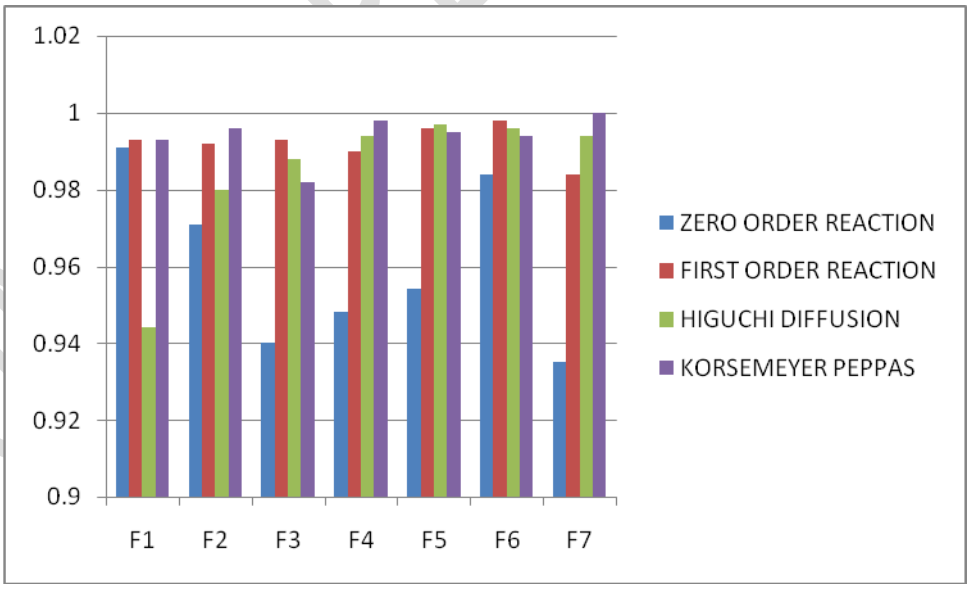

Figure 6: Drug release kinetic profile

The release rate kinetic data of F_3 formulation was found to be the best when compared to other formulation as represented in figure 3. As shown in drug release data, the drug release of F_3 formulation is best formulation suitable for first order kinetic equation with highest linearity (r^2=0.988).

As shown in figure 3, the plot for Korsmeyer-Peppas equation indicated a respectable linearity (r^2 = 0.982). The diffusion exponent “n” fitted 0.982 that indicated the diffusion mechanism is Class II transport. This indicated that the drug release is better for diffusion and dissolution.

4.CONCLUSION

In this current study, Metformin hydrochloride sustained release tablet was successfully designed by wet granulation technique. Tablets were formulated with different polymers with different composition to achieve, the target. These formulations showed good flow properties with better release of drugs and kinetics. In the *in-vitro* drug release formulation F_3, showed 72.72% of drug release in 6 hrs. The release of drug from the F_3 formulation was prolonged compared to that of other formulations. It would be desirable to study that formulation containing optimum concentration of polymer will release the drug after prolonged time interval compared with high concentration polymers. Compared to all formulation from F1 to F7, only F3 has found to be ideal concentration of the sustained release behavior. In previous study the HPMC K100 had higher viscosity shows that the formulated tablet affecting the drug release pattern in order to enhances the sustained action[26]. Similarly in our work also proves that sustained release action was achieved by HPMC K 100.

CONSENT

The patient's informed consent was obtained before the case facts were published.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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