Research Article *ISSN: 2277-8713*
Jyotsna Godbole, IJPRBS, 2012; Volume 1(6): 123-139 *IJPRBS*

ISSN: 2277-8713
INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH AND BIO-SCIENCE

FORMULATION AND EVALUATION OF BILAYER MATRIX TABLET OF ACARBOSE AND METFORMIN HYDROCHLORIDE

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IJPRBS-QR CODE

PAPER-QR CODE

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Accepted Date:

04/11/2012

Publish Date:

27/12/2012

Keywords

Metformin HCl

Acarbose

HPMC K4

HPMC K100

Sodium Starch Glycolate

Cross Carmillose Sodium

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Abstract

The aim of present study was to design the concept of bilayer matrix tablets containing Acarbose as immediate release component using sodium starch glycolate and cross carmillose sodium as super disintegrates and Metformin hydrochloride (HCl) for sustained release by using hydroxyl propyl methyl cellulose (HPMC K 4M), (HPMC K 100) and sodium carboxyl methyl cellulose (SCMC) as the matrix forming polymer and PVPK-30 as binder. Matrix tablet are the type of controlled drug delivery systems, which release the drug in continuous manner. These release the drug by both dissolution controlled as well as diffusion controlled mechanisms the half life of metformin HCl is 6.2 hrs, so an attempt was made in the direction of preparation and optimization of a combination of sustained release and immediate release in a single tablet. Tablets were prepared by wet granulation and direct compression method. Tablets were evaluated for post compression parameters. The tablets were evaluated for physico-chemical property. All the values were found to be satisfactory. Invitro release studies were carried as per USP in water and phosphate buffer of pH 6.8 using the apparatus I. The final preparation showed release of drug up to 96.75 in 8 hours. FTIR studies revealed that there is no interaction between the drug and other excipients used in the study.

INTRODUCTION

Oral route is one of the most popular routes of drug administration due to its ease of administration, patient compliance, least sterility constraints and flexible design of dosage form. Tablets are solid dosage forms containing medicinal substances with or without suitable Diluents. The tablet is the most widely used dosage form because of its convenience in terms of self-administration, compactness and ease in manufacturing. They offer safer and convenient ways of active pharmaceutical ingredients (API) administration with excellent physicochemical stability in comparison to some other dosage forms, and also provide means of accurate dosing.

A bilayer tablet is a type of multiple compressed tablets. Tablets are composed of two layers of granulation compressed together. Monogram and other distinctive marking may be compressed in the surface of the bilayer tablets. Coloring the separate layer provide many possibilities for unique tablets identity.

Bilayer tablets can be a primary option to avoid chemical incompatibilities between API by physical separation, and to enable the development of different drug release profiles (immediate release with extended release).

The aim of the study is to formulate and evaluate the bilayer matrix tablet containing sustained release layer of metformin HCL 250 mg and immediate release layer containing acarbose 25 mg for treatment of type 2 diabetes mellitus.

Rational behind the suitability of metformin HCL 250 mg SR and acarbose 25 mg IR for drug delivery system:

- The half life of metformin hydrochloride is 5-6 hrs; hence it is suitable candidate for the design of sustained release drug delivery system.
- The bilayer effect of metformin hydrochloride and acarbose was always greater than the sum of their individual.
- Patient compliance is improved when two drugs are used in single dosage forms rather than taking individual.
- By using sustained release dosage form the therapeutically effective concentration can be maintained for longer time than the convectional dosage form.

Reasons for formulating as bilayer tablets:

- Bilayer tablets are preferred when the release profiles of the drugs are different from one another i.e. in the present case 25 mg acarbose has been released immediately and the remaining 250 mg of metformin hydrochloride has to be released in sustained manner, so that therapeutic concentration can be maintained.
- Moreover metformin hydrochloride release should be less in stomach and further release should be increased in the intestine and completed within eight hours.

Hence an attempt was made to develop a bilayer matrix tablet comprising of metformin hydrochloride as sustained release and acarbose as immediate release layers within the following objective.

- ❖ To improve the patient compliance when the drug has been used in an extended release dosage form rather than convectional tablet.
- ❖ To enhance bioavailability.
- ❖ For better clinical effects.
- ❖ To reduce the incidence of adverse effects.
- ❖ Release of both drugs starts immediately.
- ❖ Combination of different release profile i.e. IR release and Sustained release can be achieved in single tablet by forming SR and IR layer.
- ❖ Reduced pill burden by reducing individual dose of two drugs due to their additive effect.
- ❖ Metformin is used for patients in the treatment of type 2 diabetes mellitus because of its favorable overall profile, including its glucose-lowering ability, weight-neutral effects, and low risk of hypoglycemia.
- ❖ Acarbose inhibits alpha-glucosidases in the small intestine, an action that delays the digestion and absorption of complex carbohydrates.
- ❖ The rational of combination therapy is to maximize the glucose-lowering effects of diabetes medications. By combining medications from different drug classes, the medications may work in two different ways to control your blood sugar. The most common combination therapy is to take two separate drugs at the same time. Two

drugs also may be combined into one pill.

MATERIALS AND METHODS

MATERIALS

Metformin HCl was obtained from Alpha Lab, Baroda and Acarbose were obtained from Aristo pharmaceuticals. The other excipients such as HPMC K15, dibasic calcium phosphate, sodium starch glycolate, talc, magnesium stearate, avicel were obtained from sagar institute of research and technology-pharmacy. HPMC K4, HPMC K100, colloidal silicon dioxide, lactose, povidone k30, sunset yellow lake colour obtained from Aristo pharmaceuticals.

METHODOLOGY:

Preparation of bilayer tablets:

LAYER I Metfromin Hydrochloride SR Granulation:

1. Sifting: metformin hydrochloride, HPMC K4, HPMC 15 cpc, sodium carboxyl methyl cellulose, dicalcium phosphate was sifted through 40 mesh sieve (stage I)

2. Binder preparation: povidone (k-30) was dissolved in water.

3. Granulation:

a) Dry mixing: the materials of stage I were mixed in pestle mortar and mixed in uniform direction.

b) Granulation: dried granules were passed through 20 mesh sieve.

c) Drying: the sifted granules were dried in an oven at 50 ^{0}C

4. Sizing: dried granules were passed through 20 mesh sieve.

5. Lubrication: colloidal silicon dioxide were sifted through 40 mesh sieve and added in stage I. Magnesium stearate and talc were sifted through 60 mesh sieve and added in stage 4 and mixed for 2 min.

LAYER II Acarbose IR Granulation: (Direct compression)

1. Sifting:

a) Acarbose were sifted through 30 mesh sieve.

b) Lactose, HPMC 15 cpc were sifted through 40 mesh sieve and sunset yellow lake were sifted through 100 mesh sieves.

2. Dry mixing: Mix acarbose with lactose, and then mix the other materials of step 1b.

3. Prelubrication: Talc was sifted through 40 mesh sieve and added to 2nd step and mixed for 5 min.

4. Lubrication: magnesium stearate was sifted through 60 mesh sieve and added to step 3 and added for 2 mins at fast speed.

Physicochemical property of prepared tablets:

The weight variations of the tablet were carried out with 20 tablets using an electronic balance. Friability was determined using 10 tablets in a Roche friabilator at a speed of 100 rpm. For each formulation the hardness was determined by using hardness tester (Pfizer). The thicknesses of each batch of tablet were measured by using verniar caliper. An invitro drug release study from the prepared bilayer matrix tablet was determined by using IP type I (paddle type)

Tablet thickness

Tablet thickness is an important characteristic in reproducing appearance and also in counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Ten tablets were taken and their thickness was recorded using calibrated dial calliper. It was measured in mm.

Tablet hardness

Hardness of tablet is defined as the force applied across the diameter of the tablet in the order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. Hardness of the tablet of each formulation was determined using Monsato Hardness tester. It was measured in kg/cm^2.

Friability:

Ten tablets were weighed and placed in the Roche friabilator and apparatus was rotated at 100 rpm. After revolutions, the tablets were dedusted and weighed again. The percentage friability was measured using formula:-

$$\% F = \{1-(W_t/W)\} \times 100$$

Where, % F = Friability in percentage,

W = Initial weight of tablets,

W_t = Weight of tablets after revolution

FTIR Spectroscopy:

FTIR spectrum was taken by scanning the sample in potassium bromide discs. The samples of pure drug and excipients were scanned individually.

IN VITRO DISSOLUTION STUDIES:

For Acarbose:

For acarbose layer, the dissolution studies were carried out in water.

Apparatus: dissolution apparataus IP Type I (Paddle type)

Medium: water, 900ml

Speed: 75 RPM.

Time: 45 min.

Temperature: 37±0.5°C

For Metformin HCl:

For metformin HCl layer, the dissolution studies were carried out in 6.8 phosphate buffer.

Apparatus: dissolution apparataus IP Type I (Paddle type)

Medium: 6.8 phosphate buffer, 900ml

Speed: 100 RPM.

Time: 1st hour, 4th hour and 8th hour.

Temperature: 37±0.5°C

Modeling and Comparison of Dissolution Profile:

Over recent years, drug release / dissolution from solid pharmaceutical dosage forms has been the subject of intense and profitable scientific developments. Whenever a new solid dosage form is developed or produced, it is necessary to ensure that drug dissolution occurs in an appropriate manner.

The quantitative analysis of the values obtained in dissolution / release tests is easier when mathematical formulas that express the dissolution results as a function of some of the dosage forms characteristics are used. In some cases, these mathematic models are derived from the theoretical analysis of the occurring process. In most of the cases the theoretical concept does not exist and some empirical equations have proved to be more appropriate.

I) Zero Order Kinetics

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly (assuming that area does not change and no equilibrium conditions are obtained) can be represented by the following equation

$$Qt = Qo + Kot$$

Where *Q* is the amount of drug dissolved in time *t*,

Q is initial amount of drug in the solution

K is the zero order release constant.

II) First Order Kinetics

This equation was first proposed by Gibaldi and Feldman (1967) and later by Wagner (1969). This model has been also used to describe absorption and/or elimination of some drugs although it is difficult to conceptualize this mechanism in a theoretical basis.

Equation for First order release kinetics is given as

$$\text{Log } Qt = \text{Log } Qo - K1t / 2.303$$

Where Qt = fraction of drug remain in dosage form

Qo = initial amount of drug in dosage form

K1 = first order release constant

III) Higuchi Model

This model is developed by Higuchi to described the dissolution of drugs in suspension from ointment bases, but is clearly in accordance with other types of dissolution from other pharmaceutical dosage form

Equation of higuchi model can be expressed as

$$ft = Q = \sqrt{D}\,(2C - Cs)\,Cs\,t$$

Where Q= amt. Of drug released in time t per unit area

C= initial drug concentration

Cs = drug solubility in the matrix media

D = diffusivity of drug molecules in the matrix substances

IV) Korsmeyer-Peppas model

Korsmeyer et al. (1983) developed a simple, semi- empirical model, relating exponentially the drug release to the elapsed time (*t*)

Equation is given as follows

$$Mt / M\infty = a\,tn$$

Where a = constant incorporating structural and geometrical characteristics of dosage form

n = release exponent indicative of drug release mechanism.

Mt / M∞ = release fraction of drug is the function of time.

RESULT AND DISCUSSION

The FTIR spectrum of metformin and acarbose was shown in the Figure 1 and 2. The spectra revealed that there was no interaction between the drug and excipients.

IN VITRO DISSOLUTION OF DRUG:

Cumulative percentage drug release of different formulations of drug:

In order to achieve the development of a combination of a conventional and sustained release dosage forms, currently the bilayer technology with multiple layers having a rapid and sustained phase has been investigated. This formulation can be used for the treatment of type II Diabetes Mellitus.

Compatibility studies:

The IR spectrum of pure Metformin HCl, Acarbose and other exepients was compared with the IR spectrum of formulated Metformin HCl sustained release and immediate release of Acarbose tablets. The IR spectrums of formulation were matching with the IR spectrum of pure Metformin and Acarbose.

There is no appearance or disappearance of any characteristic peaks. This shows that there is no interaction between the drug, exepients and polymer used in the tablets.

CONCLUSION

From the literature Review, Metformin HCl and Acarbose individual dosage form was used in the management

Of diabetes mellitus. Combination of Acarbose as immediate release layer and Metfromin HCl as sustained release layer improves the patient compliance. Sustained release, sustained action, prolonged action, controlled action, extended release action, timed release are terms used to identify drug delivery system that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. In the case of injectable dosage forms, this period may vary from day to months. In the case of orally administered forms, however, this period is measured in hours and critically depends on the residence time of the dosage forms in the GI tract. The term CR

has become associated with those systems from which therapeutic agents may be automatically delivered at predefined rates over a long period of time. Products of this type have been formulated for oral, injectables and topical use.

Bilayer tablets can be a primary option to avoid chemical incompatibilities between API by physical separation, and to enable the development of different drug release profiles (immediate release with extended release) Time release technology, also known as sustained-release (SR), sustained-action (SA), extended-release (ER, XR, or XL), time-release or timed-release, controlled-release (CR), modified release (MR), or continuous-release (CR or Contin), is a mechanism used in pill tablets or capsules to dissolve slowly and release a drug over time. The advantages of sustained-release tablets or capsules are that they can often be taken less frequently than immediate-release formulations of the same drug, and that they keep steadier levels of the drug in the bloodstream. Today, most time-release drugs are formulated so that the active ingredient is embedded in a matrix of insoluble substance(s), such that the dissolving drug must find its way out through the holes in the matrix. Some drugs are enclosed in polymer-based tablets with a laser-drilled hole on one side and a porous membrane on the other side. Stomach acids push through the porous membrane, thereby pushing the drug out through the laser-drilled hole. In time, the entire drug dose releases into the system while the polymer container remains intact, to be excreted later through normal digestion.

Formulation of bilayer tablet is a need of today with the variety of reasons:

- Proper utilization of the therapeutic dose.
- To avoid the incompatibility (physical) between the two synergistic drugs.
- To achieve the drug release as per the biological clock basis.
- Patent extension.
- Economical as compared to other control and target drug delivery system.

Oral drug delivery is the most popular as compared to the other route of administration. Bilayer tablets get populated in the future due to its ease in the productivity as well as economically as

compared to the others target drug delivery system.

ACKNOWLEDGEMENT

The authors are thankful to the Sagar institute of research and technology-pharmacy, Bhopal (M.P), India for their support and cooperation in carrying out the research work.

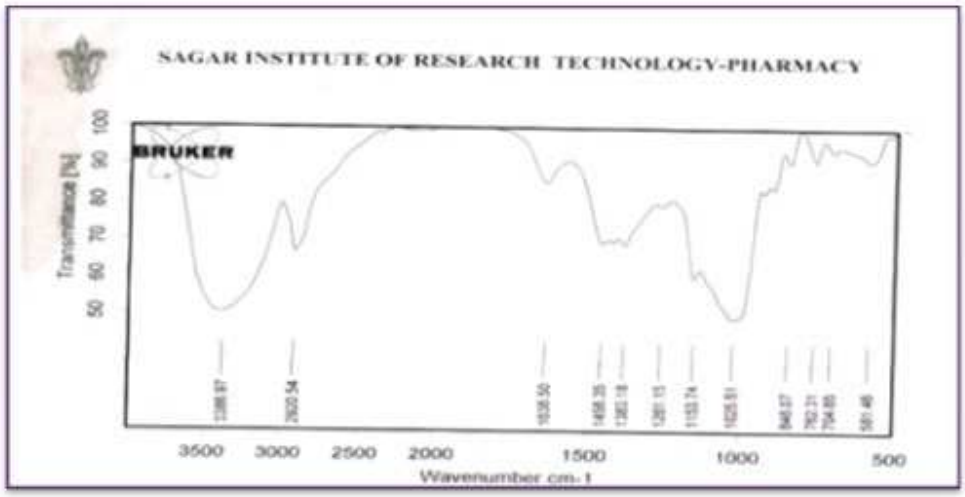

Figure 1 FTIR Spectra of pure drug (Acarbose)

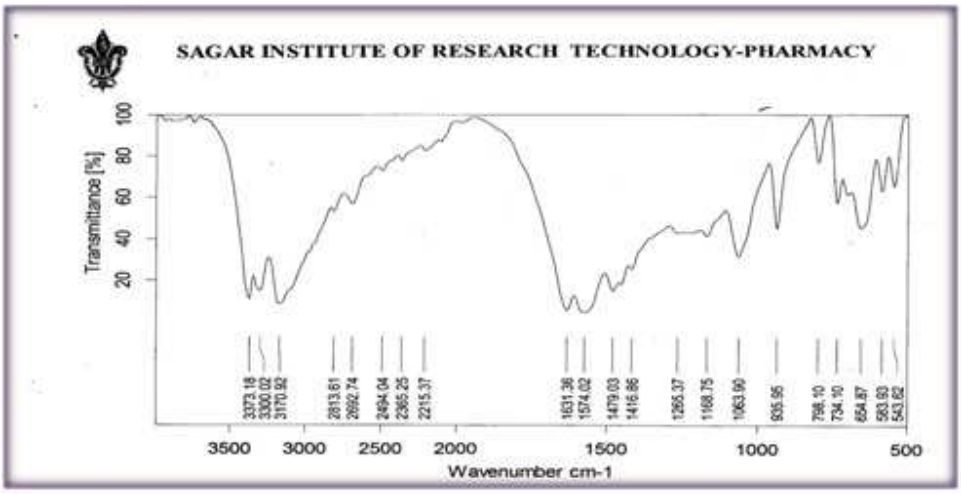

Figure 2 FTIR spectra of pure drug (Metformin HCL)

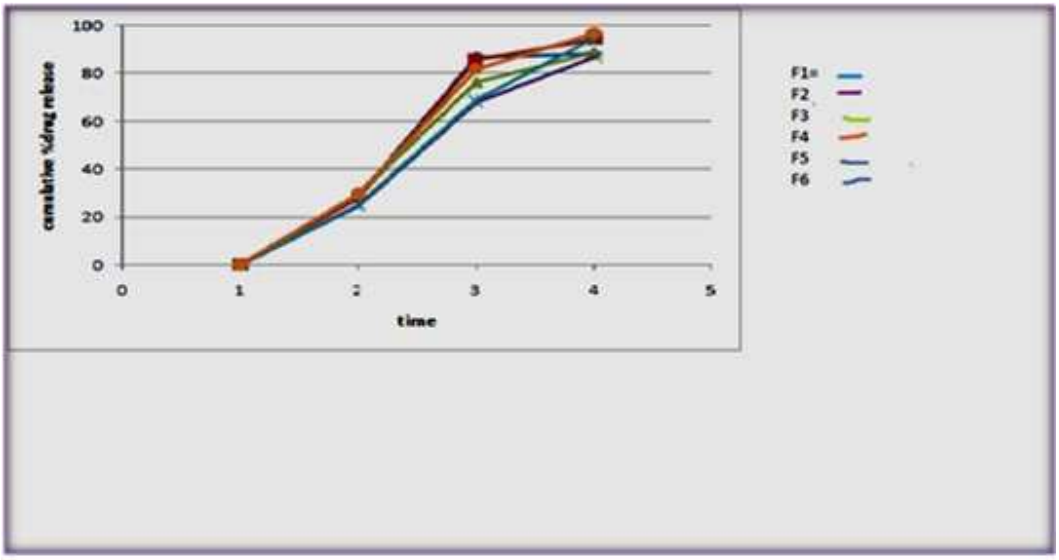

Figure 3 CPR of different formulations of Metformin HCL SR layer (layer I)

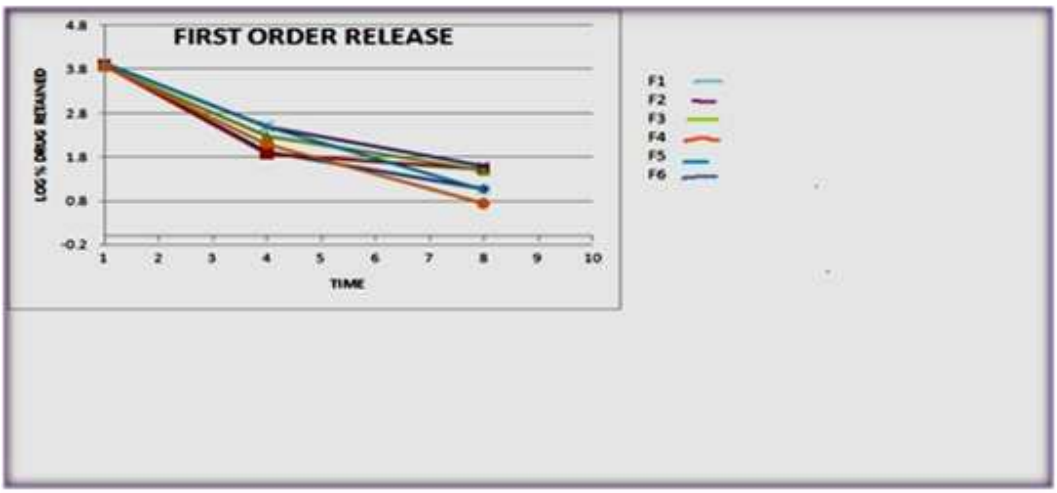

Figure 4 Plots showing first order release rate of different formulations

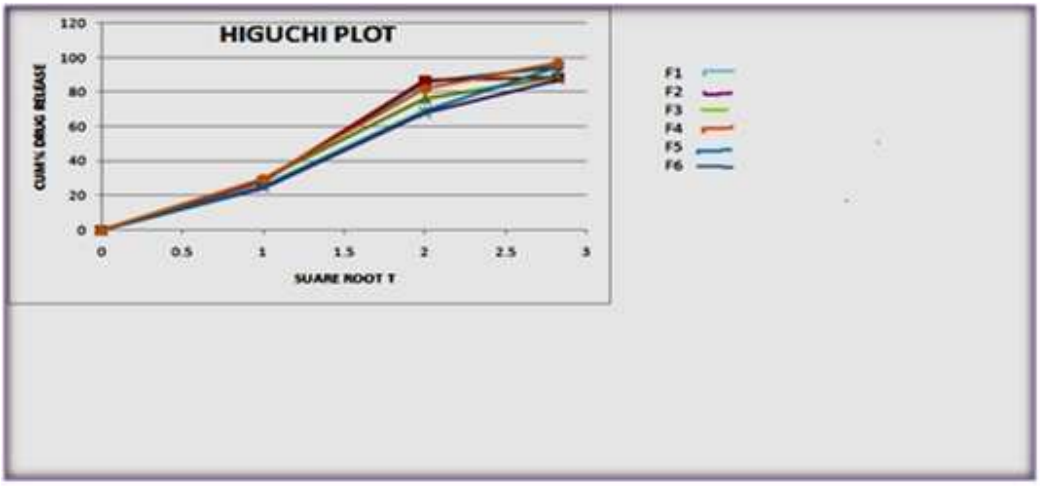

Figure 5 Plots showing Higuchi plot of different formulations

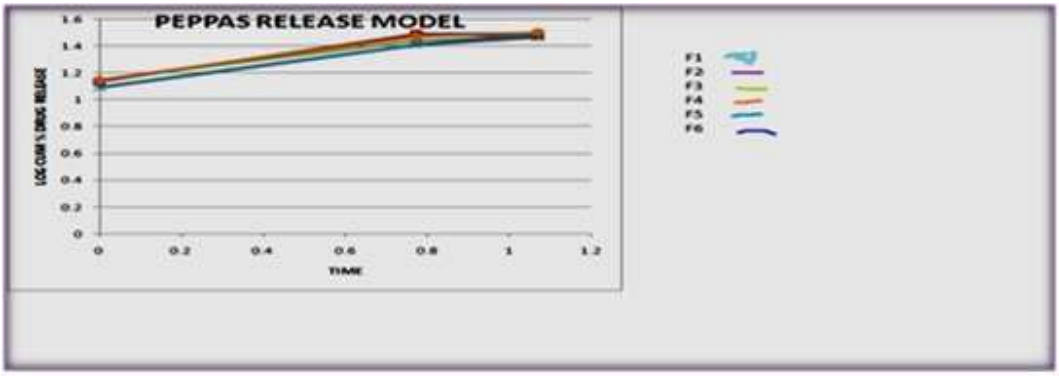

Figure 6 Plots showing Peppas model of different formulations

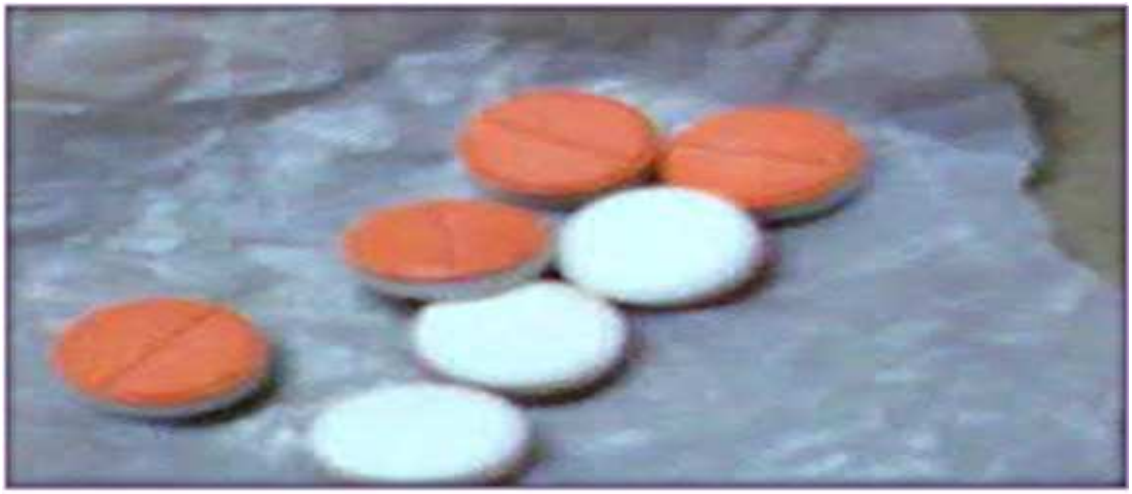

Figure 7 Photograph of Bilayer Tablet

Table 1

Composition of Metformin Sustained Release Layer (LAYER I)

S. NO	INGREDIENTS	F1	F2	F3	F4	F5	F6
1.	Metformin HCL	250	250	250	250	250	250
2.	DCP	150.36	108.3	22.88	103.13	55.85	23
3.	HPMCK4	5	5	25	25	25	25
4.	HPMCK100	-	-	10	25	30	32
5.	SCMC	-	42.5	42.25	84.85	100	100
6.	Povidone (k-30)	4	-	4	4	4	4
7.	Colloidal silicon dioxide	2.5	2.5	2.5	2.5	2.5	2.5
8.	Talc	4	4	4	4	4	4
9.	Calcium carbonate	4.5	4.5	4.5	4.5	4.5	4.5
10.	Purified water	qs	qs	qs	Qs	Qs	Qs
11.	**Total weight**	**500**	**500**	**500**	**500**	**500**	**500**

Table 2

Composition Of Acarbose Immediate Release Layer (LAYER II)

S. NO	INGREDIENTS	F1	F2	F3	F4	F5	F6
1.	Acarbose	25	25	25	25	25	25
2.	PVPK-30	2	2	-	-	-	-
3.	SSG	4.5	6	7.5	12	12	12
4.	CCS	2	3	7.5	12	10	10
5.	Lactose	20	65.31	83.5	90	95.33	100
6.	HPMC 15 CPS	2.5	2.5	-	-	-	-
7.	Magnesium stearate	1	1	1	1	1	1
8.	Talc	1.6	1.6	1.6	1.6	1.6	1.6
9.	Sunset yellow lake	1	1	1	1	1	1
10.	Purified water	Qs	qs	qs	Qs	Qs	Qs
11.	**Total weight**	**150**	**150**	**150**	**150**	**150**	**150**

Table 3

Physicochemical Property of Prepared Bilayer Tablet Containing Metformin as Sustained Release and Acarbose as Immediate Release Component.

S.NO	Weight variation± SD	Hardness in mm	Thickness in kg/cm^2	Drug content	
				Acarbose	Metformin
1	0.48±0.03	6.3±0.02	6.3±0.17	80.4±1.39	86.3±1.53
2	0.59±0.03	6.2±0.02	6.3±0.18	84.2±1.61	88.37±1.53
3	0.33±0.02	6.5±0.01	6.2±0.21	86.6±1.65	88.79±2.34
4	0.21±0.04	6.4±0.04	6.4±0.32	90.1±1.79	86.95±1.56
5	0.44±0.02	6.4±0.03	6.4±0.12	97.3±1.19	94.5±1.63
6	0.42±0.02	6.2±0.02	6.3±0.21	98.3±1.05	96.75±2.13

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