Original Article

Design and development of bilayer tablet for immediate and extended release of acarbose and metformin HCl

Abstract

The present investigation studied a novel Bilayer tablet having extended release (ER) system of metformin HCl (M.HCl) with Eudragit RS 100 and RL 100 and immediate release (IR) system of Acarbose with PVP K30 and PEG 6000 in different ratios using solvent evaporation technique. Solid dispersions (SDs) were characterized by Fourier Transform-Infra Red spectroscopy, Diffrential Scanning Calorimetry, X-Ray Diffractometry and Scanning Electron Microscopy. Selected SD system was subjected to Bilayer tablet preparation by direct compression. Compressed tablets were evaluated for physical parameters, drug release and stability. SEM studies suggested the homogenous dispersion of the drug in polymers. FT-IR studies confirmed the formation of hydrogen bonding between the drug and polymer. XRD and DSC suggested the amorphous nature of the drug in SDs. All tablet formulations showed compliance with pharmacopoeial standards. *In-vitro* dissolution kinetics followed the Higuchi model via a non-fickian diffusion controlled release mechanism after the initial burst release. Stability studies conducted for optimized formulation did not show any change in the physical properties, drug content and drug release. Bilayer tablets showed an IR effect to provide the loading dose of the drug, followed by ER effect for 12 h, indicating a promising potential of the M.HCl and Acarbose Bilayer tablet as an alternative to the conventional dosage form.

Key words:
Acarbose, bilayer tablet, metformin HCl, solid dispersion

Introduction

Metformin HCl (M.HCl) is the sole member of the biguanide class of medications in the United States. It replaced another biguanide, Phenformin, which was removed from the market because of a propensity for lactic acidosis in 1975. M.HCl exerts its effects the primarily by decreasing the hepatic glucose output and has a comparatively lesser effect in increasing the insulin sensitivity. Isotope studies suggest that hepatic glucose output is reduced primarily through inhibition of gluconeogenesis, which may be reduced by as much as 75%. In patients with normal renal function and who are otherwise healthy, M.HCl does not increase plasma lactic acid levels or rate of turnover. The major clinical effect of M.HCl is to decrease the fasting glucose levels, thereby reducing the hemoglobin A1c. The degree of clinical effect varies in the individual patients, but most of the patients experience a reduction in A1C of ~1.5 percentage points. Lactic acidosis is a rare but potentially fatal complication of Metformin therapy. Incidence of this complication is very low: <1 case per 100,000 treated the patients.[1]

Acarbose belongs to the class of alpha-glucosidase inhibitors. It inhibits intestinal enzymes that digest carbohydrate, thereby reducing the carbohydrate digestion after meals. This lowers the postprandial glucose elevation in diabetics.

Acarbose in combination with M.HCl has the potential to delay the diabetes complications through improvement of metabolic control. There was also a favorable effect on fasting blood glucose levels. Reduced glucose toxicity through decreasing the postprandial blood glucose

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elevations and a beneficial effect of the increased late rise in glucagon-like peptide 1 on reducing fasting blood glucose are possible mechanisms for this effect. Acarbose and M.HCl are both associated with beneficial effects on hyperglycemia, hyperinsulinemia, body weight, and, in some studies, triglyceride levels. Because these factors are part of a cluster of risk factors for cardiovascular disease, combining the two drugs may be useful.

Solid dispersion (SD) is defined as "the dispersion of one or more active ingredients in an inert matrix at solid-state prepared by melting (fusion), solvent or melting-solvent method" was first introduced by Sekiguchi and Obi (1961). Since then, solid dispersion-containing drug delivery systems prepared by solvent-emulsion evaporation, hot-melting, solvent evaporation, coprecipitation, spray drying, supercritical, and co-grounding, etc. have been reported in the literature for use in improvement of bioavailability and controlled delivery of the drugs.[2]

The layered tablet concept has been utilized to develop the controlled-release formulations.[3-6] Such a tablet is considered as a biphasic delivery system that is designed to release the drug at two different rates and is usually composed of a fast-release layer combined with single or double sustained-release layers.[7,8] Generally, conventional controlled-release dosage forms delay the release of drugs and do not provide a rapid onset of action after oral administration.[9,10] Hence, the layered tablets offer a pharmacokinetic advantage over conventional controlled-release dosage forms as the drug is quickly released from the fast-release layer leading to rapid rise of drug plasma concentration followed by continuation of drug release from the sustained-release layer.[11]

In order to form the SDs of M.HCl, polymers such as Eudragit RS 100, Eudragit RL 100 were used and in order to form Acarbose SDs many compounds such as polyethylene glycol 6000 (PEG 6000), polyvinylpyrrolidone K30 (PVP K30), were reported to be used as carriers, which could also modify the release rate of both the drugs. Several SDs containing different proportions of carriers were prepared and their physicochemical properties were tested. Furthermore, their Bilayer tablets were formed and evaluated.

Materials and Methods

Materials

M.HCl was supplied from Ipca laboratories, Dehradoon and was Acarbose supplied from Windlas Biotech, Dehradoon. The Eudragit RS 100 and RL 100 utilized in this study were obtained from Evonik Industries, Mumbai. All solvents and chemicals were of analytical reagent grade used as obtained.

Methods

Drug identification test

UV spectrophotometric studies

Standard stock solution was prepared by dissolving M.HCl in double distilled water, phosphate buffer of pH 7.4 and 6.8 to make final concentration of 1 mg/mL. Different aliquots were taken from stock solution and diluted with double distilled water, pH 6.8 and pH 7.4 phosphate buffers respectively to prepare the series of concentration from 2-20 μg/mL. The absorption λ_{max} was measured between 400 nm to 200 nm.

The λ_{max} of Acarbose was determined by dissolving Acarbose in phosphate buffer of pH 1.2, 6.6 and 7.4 respectively, and then 2 mL of NaOH and 0.001 mg $KMnO_4$ were added. The solution was heated and volume was made with buffer of pH 1.2, 6.6 and 7.4 respectively to obtain the concentration of 1 mg/mL. Several dilutions were prepared and λmax was scanned between 400 nm to 200 nm using UV spectrophotometer.

Preparation of calibration curve

Calibration curve of M.HCl was prepared by dissolving 20 mg of drug in 100 mL of three different solvents i.e. double distilled water, phosphate buffer of pH 6.8 and 7.4 respectively to obtain the concentration of 200 μg/mL. Four mL of the above solution was pipetted out and volume was made up to 40 mL to obtain the concentration of 20 μg/mL. From the above prepared solution several dilutions were made in the concentration range of 2-2 μg/mL. The absorbance was measured at 232.4 nm.

Calibration curve of Acarbose was prepared in three different solvents i.e. phosphate buffer of pH 1.2, 6.6, 7.4. 5 mg of the drug was dissolved in 1 mL of each buffer. To this, 1 mL of NaOH was added and volume was made up to 10 mL to obtain the concentration of 500 μg/mL. To the above prepared solution 0.001 mg of $KMnO_4$ was also added. The above solution was further diluted to obtain the concentration of 50 μg/mL. Further dilutions were made in the concentration range of 5-50 μg/mL. The absorbance was measured at 299.4 nm.

Statistical test

Calibration curve data was subjected to linear regression analysis to study the linearity and various optical characteristics were calculated.[12]

Drug-excipients compatibility studies

It is an investigation of the physical and chemical properties of the individual drug substance alone and after combining with the excipients. M.HCl and Acabose were taken individually in a glass vial, both M.HCl along with various excipients and Acarbose with various excipient in different ratios were taken in glass vial. All the above mixtures of the drug substances were kept at various accelerated condition

(30^{0}C/65% RH and 40^{0}C/75% RH) in stability chamber. It was carried out for one month in the open and closed glass vials. At the time intervals of 2 weeks (till 4th weeks), the samples were withdrawn and checked out for any changes in the physical character.[13]

Preparation of SDs of M.HCl and acarbose

Solvent evaporation

The required amount of M.HCl and the carriers (Eudragit RS 100, Eudragit RL 100) in the ratios as shown in Table 1 were dissolved in sufficient volume of ethanol with continuous stirring. The solvent was then completely evaporated at 45º C with continuous stirring to obtain the dry mass. The dried mass was pulverized, passed through 44 mesh sieve and stored in desiccator until used for further studies.

For the preparation of Acarbose SD, the required amount of Acarbose and the carrier (PVP K30, PEG6000) in the ratios as shown in Table 2 were dissolved in sufficient volume of methanol with continuous stirring. The solvent was then completely evaporated at 45 º C with continuous stirring to obtain the dry mass. The dried mass was pulverized passed through 44 mesh sieve and stored in desiccator until used for further studies.

Table 1: Composition of SD of M.HCl

Formulation Code	Carrier	Drug: Carrier	Method
MF1	Eudragit RL 100	1:1	Solvent evaporation
MF2		1:2	
MF3		1:5	
MF4	Eudragit RS 100	1:1	Solvent evaporation
MF5		1:2	
MF6		1:5	
MF7	Eudragit RL 100,	1:1:1	Solvent evaporation
MF8	Eudragit RS 100	1:1:2	
MF9		1:2:1	
MF10	Eudragit RL 100	1:1	Physical mixture
MF11		1:2	
MF12		1:5	
MF13	Eudragit RS 100	1:1	Physical mixture
MF14		1:2	
MF15		1:5	

Table 2: Composition of SD of Acarbose

Formulation code	Carrier	Drug: carrier	Method
AF1	PVP K 30	1:1	Solvent evaporation
AF2		1:2	
AF3		1:4	
AF4	PEG 6000	1:1	Solvent evaporation
AF5		1:2	
AF6		1:4	
AF7	PVP K 30	1:1	Physical mixture
AF8		1:2	
AF9		1:4	
AF10	PEG 6000	1:1	Physical mixture
AF11		1:2	
AF12		1:4	

Preparation of physical mixtures of drug-carrier

Physical mixtures of M.HCl were obtained by blending the components in a glass mortar. M.HCl and two different carriers (Eudragit RL 100 and Eudragit RS 100) in different ratios, were accurately weighed and passed through a sieve no. 40 (0.42 mm), mixed well in the mortar, shifted through the same sieve and stored in desiccator under vacuum. The compositions of physical mixture are shown in Table 1.

Physical mixtures of Acarbose were obtained by blending Acarbose and two carriers (PEG 6000, PVP K 30) in different ratios in a mortar. They were then passed through a sieve no. 40, mixed well in the mortar, shifted through the same sieve and stored in desiccator under vacuum.[14] The compositions of the physical mixture are shown in Table 2.

Drug content study

For M.HCl, 10 mg of SD was accurately weighed and dissolved in 10 mL of phosphate buffer, pH 7.4 and filtered. Sample (1 ml) was diluted 100 times with buffer and absorbance was measured with a UV spectrophotometer at 232.4 nm. The M.HCl content was calculated using the calibration curve.

For Acarbose, 10 mg of SD was accurately weighed and dissolved in 10 ml of phosphate buffer, pH 7.4 and filtered. Sample (1 ml) was diluted 100 times with buffer and absorbance was measured with a UV spectrophotometer at 299.4 nm. The Acarbose content was calculated using the calibration curve.[14]

Characterization of SDs

X-ray powder diffractometry (XRD)

Diffraction patterns of physical mixtures, drug, SDs and polymers were recorded with a PW 3040/60 X' Pert PRO, Netherland. A voltage of 40 KV and a current of 30 mA for the generator were used, with Cu as the tube anode material. The solids were exposed to Cu-Kα radiation (α1 = 1.54060 Å and α2 = 1.54439 Å, with a α1/α2 ratio of 0.5), over a range of 2θ angles from 10 ˚C to 60 ˚C, at an angular speed of 1^0 (2θ) per minute.

FT-IR spectroscopy

IR spectra of pure drug and polymers and of SDs and physical mixtures were obtained using FT-IR-Perkin Elmer (UK). Sample was spread over cuvette and the IR spectrum was obtained. Scanning range was 400 to 4000 cm^{-1} with a resolution of 1 per cm^{-1}. The IR spectra obtained were studied for possible drug excipients interaction.

Scanning Electron Microscopy (SEM)

Morphology of pure drug, polymers, physical mixtures and SD particles were characterized by scanning electron

microscopy using LEO 435 VP, UK. Samples were fixed on supports with carbon glue and coated with gold using the gold sputter model in a high vacuum evaporator. Samples were then observed with scanning electron microscopy.

Differential scanning calorimetry (DSC)

Thermal analysis was performed on the drug, SDs, physical mixtures and polymers using a PERKIN — ELMER DSC-7. Samples (10-15 mg) were weighed and sealed into 40 μL aluminium pans. DSC runs were conducted over a temperature range of 70 °C to 250 °C at a rate of 10 °C/minute in nitrogen atmosphere.

Flow properties of SDs

Flow properties of SDs were determined by calculating the angle of repose, bulk density, compressibility index and Hausner's ratio.

Determination of in-vitro drug release of SDs

Dissolution tests were performed under the sink condition using USP standard dissolution apparatus with a basket stirrer. The dissolution medium (900 mL of phosphate buffer solution with pH 7) was maintained at 37 ± 0.5 °C and stirred at 100 rpm. At predetermined intervals, 5 mL of samples was withdrawn and equal volume of fresh dissolution medium was used to maintain a constant volume. The samples were diluted, filtered and analyzed using UV spectrophotometer at 232.4 nm for M.HCl and 299.4 nm for Acarbose. The tests were performed three times to check repeatability.[15]

Evaluation of release kinetics

To know the mechanism of the drug release from these formulations, the data were treated according to first order (log cumulative percentage of drug remaining versus time), Higuchi's (cumulative percentage of the drug released versus square root of time), Hixon Crowell (cube root of percentage of the drug remaining versus time) and Korsmeyer's (log cumulative percentage of the drug released versus log time) equations along with a zero-order (cumulative percentage of the drug release versus time) pattern.[16]

Selection of solid dispersion

On the basis of release profiles, model dependent and model independent parameters, SD of M.HCl with Eudragit RL 100 and Eudragit RS 100 (1:1:2) prepared by solvent evaporation technique (MF8) and SD of Acarbose and PVP K30 (1:4) prepared by solvent evaporation technique were selected for the preparation of Bilayer tablet.

Preparation of bilayer tablets

Optimized formulations of M.HCl extended release (ER) SD (MF8) and Acarbose immediate release (IR) SD (AF3) were selected and final Bilayer tablets were prepared according to the following formula [Tables 3 and 4]. Final Bilayer tablets were compressed as one layer only for M.HCl and second layer for Acarbose using 19.8 x 8.7 mm round shape punch in 27 station tablet compression machine (Cadmach, India). The tablet was compressed as Bilayer tablet using both M.HCl and Acarbose powder. In this, M.HCl powder were introduced first into the die cavity and a slight precompression was made so that the layer was uniformly distributed after that Acarbose powder was added and a final compression was made.[1,13] The photograph of Bilayer tablet is shown in Figure 1.

Evaluation of prepared bilayer tablets

Drug content

Ten tablets were weighed individually, crushed and the drug was extracted in phosphate buffer of pH 7.4. The solution was filtered and the drug content was determined spectrophotometrically at λ_{max} of 299.4 nm and 232.4 nm after suitable dilution.[11]

Thickness

Twenty tablets from the representative sample were randomly taken and individual tablet thickness was

Table 3: Composition of ER layer of M.HCl

Ingredients (mg)	MB1
Solid dispersion eq. to M.HCL	854.5
MCC	441
Magnesium stearate	2
Talc	2
Sunset yellow	0.5
Total weight	1300

Table 4: Composition of IR layer of Acarbose

Ingredients (mg)	AB1	AB2	AB3	AB4
Solid dispersion eq. to Acarbose	30	30	30	30
Carboxymethyl cellulose sodium	4	6	8	10
MCC	162	160	158	156
Magnesium stearate	2	2	2	2
Talc	2	2	2	2
Total weight	200	200	200	200

Figure 1: Photograph of Bilayer tablet

measured by using vernier calipers. Average thickness and standard deviation values were calculated.

Hardness

Tablet hardness was measured by using Monsanto hardness tester. From each batch six tablets were measured for the hardness and average of six values was noted along with standard deviations.

Friability test

From each batch, ten tablets were accurately weighed and placed in the friability test apparatus (Roche friabilator). Apparatus was operated at 25 rpm for 4 minutes and tablets were observed while rotating. The tablets were then taken after 100 rotations, dedusted and reweighed. The friability was calculated as the percentage weight loss.

% Friability = (W1 – W2) x 100/W1

Where, W1 = Initial weight of the 20 tablets.

W2 = Final weight of the 20 tablets after testing.

Weight variation test

To study the weight variation individual weights (WI) of 20 tablets from each formulation were noted using electronic balance. Their average weight (WA) was calculated. Percent weight variation was calculated as follows. Average weights of the tablets along with standard deviation values were calculated.

% weight variation = (WA–WI) x 100/ WA

Swelling behavior

Bilayer tablet was weighed and kept in the petridish under standard set of conditions. The tablets were removed from the petridish and swollen weight of tablet was determined.[16] Swelling (%) was calculated according to the following formula,

S% = 100(H3-H2)/H2

Where,

H1 = Initial tablet weight

H2 = Dry weight of tablet

H3 = swelled tablet weight

In-vitro drug release of bilayer tablets

The release of Bilayer tablet was determined using USP dissolution apparatus II at 50 rpm. The dissolution was studied using 900 mL of phosphate buffer pH 7.4. The temperature was maintained at 37 ± 0.5 ˚C. The samples for IR layer were withdrawn at different time intervals, i.e. 15, 30, 45, 60 mins, filtered through Whatman filter paper and replaced by an equal volume of dissolution medium. Samples were suitably diluted and analyzed at 299.4 nm. The percentage of Acarbose release was calculated.

For ER layer samples were collected at different time interval i.e. 0.5, 1, 2, 4, 6, 8, 10 and 12 h, filtered through Whatman filter paper and replaced by an equal volume of dissolution medium. Samples were diluted and analyzed at 232.4 nm by using UV spectrophotometer.[17] The percentage of M.HCl release was calculated.

Release kinetics

To know the mechanism of the drug release from these formulations, the data were treated according to first order (log cumulative percentage of the drug remaining versus time), Higuchi's (cumulative percentage of the drug released versus square root of time), Hixon Crowell (cube root of percentage of the drug remaining versus time) and Korsmeyer's (log cumulative percentage of the drug released versus log time) equations along with a zero-order (cumulative percentage of the drug release versus time) pattern.[16]

Similarity factor

Moore and Flanner suggested a simple model independent approach uses a similarity factor to compare dissolution profiles. The similarity factor (f2) was calculated using the following Eq.

$$f_2(\%) = 50 \log\left\{\left[1+\frac{1}{n}\sum_{t=1}^{n} w_t(R_t - T_t)^2\right]^{-0.5} \times 100\right\}$$

Where, log is logarithm to base 10, n is number of sampling time points, is summation over all time points, *wt* is an optional weight factor, R_t is dissolution at time point t of the reference, and T_t is dissolution at time point t of the test. For curves to be considered similar, f2 values should be closed to 100%. In this study, all the values are to be treated equally. w_t is taken as unity.[18]

Statistical analysis

Analysis of variance (ANOVA) was used to determine statistically significant differences between results. Results with *P*-values < 0.05 were considered statistically significant.[19]

Stability of bilayer tablets

Stability studies were performed according to ICH and WHO guidelines. Optimized tablets were Al/PVC packed and kept for 3 months at 45 °C and 75% RH and 37 °C in stability chamber. At the end of studies, tablets were evaluated for physical properties, *in- vitro* drug release and drug content.[20]

Result and Discussion

Drug identification tests

UV spectrophotometric study

M.HCl

UV spectrophotometric study was carried out in different media [double distilled water, phosphate buffer (pH 6.8 and pH 7.4)] in a scanning range of 200 to 400 nm. The λ_{max} obtained was recorded [Table 5].

Acarbose

UV spectrophotometric study was carried out in different media [0.1 N HCl (pH 1.2), phosphate buffer (pH 6.6 and

pH 7.4)] in a scanning range of 200 to 400 nm. The λ_{max} obtained was recorded [Table 6].

Preparation of calibration curve

M.HCl

The absorbance values of standard concentrations of 4-26 µg/mL were plotted and linearity water and phosphate buffer (pH 6.8) [Table 7] when analyzed at 232.4 nm.

Acarbose

The absorbance values of standard concentrations of 10-50 µg/mL were plotted and linearity was observed with an r^2 = 0.998 for phosphate buffer (ph 7.4), r^2 = 0.999 for 0.1 N HCl (pH 1.2) and phosphate buffer (pH 6.6) [Table 8] when analyzed at 299.4 nm.

Statistical test

Caliberation curve data was subjected to linear regression analysis and optical characteristics were calculated. M.HCl and Acarbose obeyed Beer and Lambert's law in concentration range of 4-26 µg/mL and 10-50 µg/mL respectively. The comparative optical characteristics of M.HCl and Acarbose are shown in Tables 9 and 10 respectively.

Drug-excipients compatibility studies

In drug-excipients compatibility studies, the samples which were kept at various accelerated conditions were withdrawn and carried out physical characteristics evaluation like color change at different intervals. From the results of compatibility studies, we observed that there was no incompatibility in drugs alone or with excipients.

Characterization of solid dispersion systems

FT-IR spectroscopy

Physical mixtures with the same composition of SDs were tested as a reference. In fact observations indicated that most interaction between M.HCl and Eudragit, Acarbose and PVP K30 occurred in solution and not after a simple grinding of two components. There was no appearance and disappearance of any characteristic peaks for both M.HCl and Acarbose. This showed that there was no interaction between the drug and polymers. However in comparison with their physical mixtures, M.HCl and Acarbose both gave a broad band in their respective SDs. This result suggested the presence of intermolecular hydrogen bonding between M.HCl and Eudragit, Acarbose and PVP K30 in SDs [Figures 2 and 3].

X-ray powder diffraction (XRD)

XRD spectra of M.HCl SD i.e. MF8 and its physical mixture are shown in Figure 4. In diffractograms, the peak position (angle of diffraction) is indicative of a crystal structure and the peak height is a measure of the sample crystallinity. The diffractograms of pure M.HCl and pure Eudragit RS and RL 100 exhibited a series of intense peaks which are indicative of their crystallinity. The diffractogram of physical mixture

Table 5: Comparative λ_{max} of M.HCl

Solvents	λ_{max}
Double distilled water	232.4 nm
Phosphate buffer (pH 6.8)	232.4 nm
Phosphate buffer (pH 7.4)	232.4 nm

Table 6: Comparative λ_{max} of Acarbose

Solvents	λ_{max}
0.1 N HCl (pH 1.2)	299.4 nm
Phosphate buffer (pH 6.6)	299.4 nm
Phosphate buffer (pH 7.4)	299.4 nm

Table 7: Data of standard plot of M.HCl in double distilled water, phosphate buffer (pH 6.8 and ph 7.4) at 232.4 nm

Concentrations (µg/mL)	Absorbance*		
	Double distilled water	Phosphate buffer (pH 6.8)	Phosphate buffer (pH 7.4)
0	0	0	0
2	0.243	0.169	0.390
4	0.424	0.386	0.729
8	0.855	0.806	1.315
12	1.288	1.184	1.908
16	1.706	1.595	2.577
20	2.132	1.940	3.081

*Average of 3 determinations

Table 8: Data of standard plot of Acarbose in 0.1 N HCl (pH 1.2), phosphate buffer (pH 6.6 and ph 7.4) at 299.4 nm

Concentrations (µg/mL)	Absorbance*		
	N HCl (pH 1.2)	Phosphate buffer (pH 6.6)	Phosphate buffer (pH 7.4)
0	0	0	0
5	0.018	0.018	0.076
10	0.035	0.035	0.187
20	0.065	0.065	0.423
30	0.098	0.098	0.612
40	0.124	0.124	0.827
50	0.154	0.154	0.996

*Average of 3 determinations

Table 9: Comparative optical characteristics of M.HCl

Solvents	Concentration (µg/mL)	Correlation coefficient	Regression equation
Double distilled water	4-26	0.999	Y = 0.106 x + 0.009
Phosphate buffer (pH 6.8)	4-26	0.999	Y = 0.098 x – 0.004
Phosphate buffer (pH 7.4)	4-26	0.998	Y = 0.153 x + 0.069

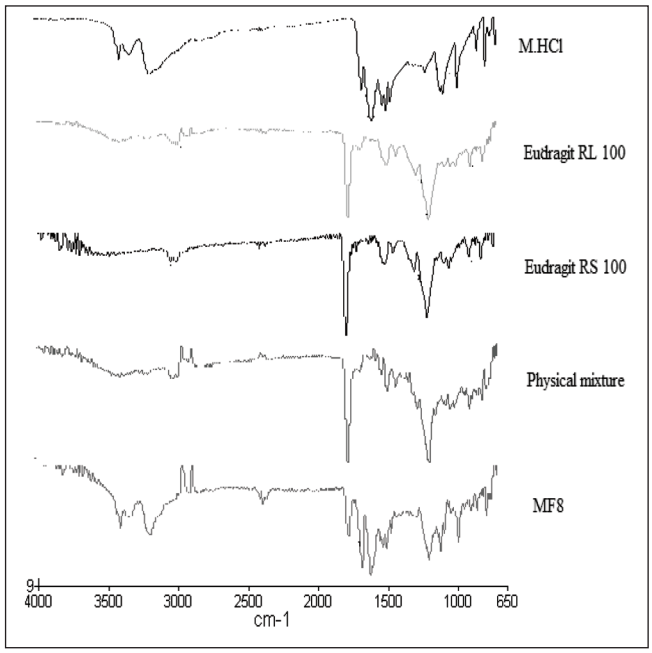

Figure 2: FT-IR Spectrum of M.HCl, Eudragit RL100, Eudragit RS 100, physical mixture, MF8

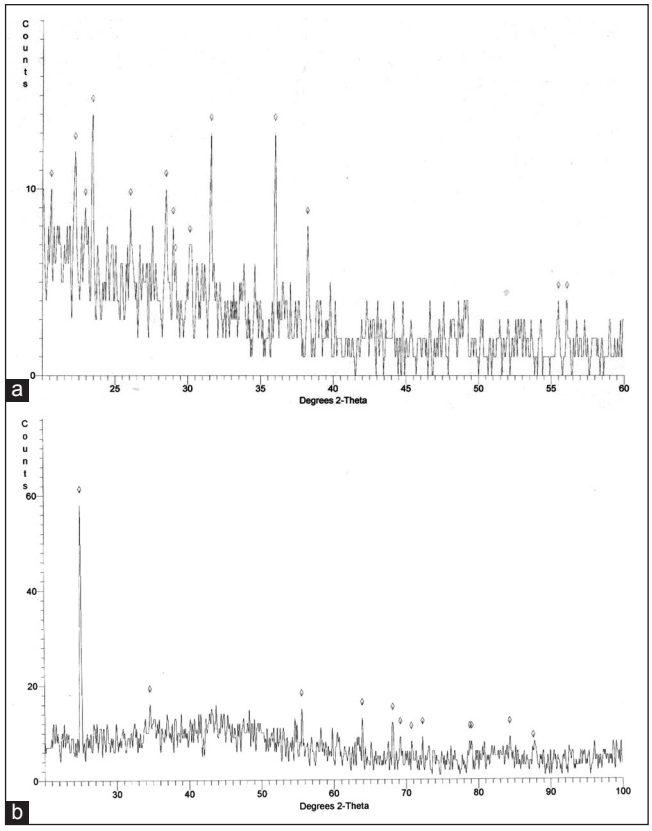

Figure 4: X-ray diffraction patterns of physical mixture (a) and MF8 (b)

was practically a simple superposition of each component, indicating the presence of M.HCl in a crystalline state and no formation of a new structure. The SD (MF8) showed a

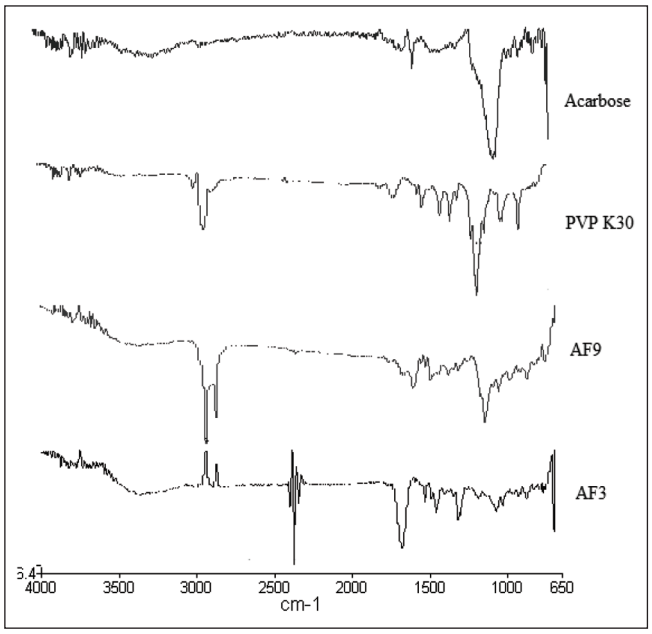

Figure 3: FT-IR Spectrum of Acarbose, PVP K30, AF9 and AF3

Table 10: Comparative optical characteristics of Acarbose

Solvents	Concentration (µg/mL)	Correlation coefficient	Regression equation
N HCl (pH 1.2)	10- 50	0.999	Y=0.003 x+0.002
Phosphate buffer (pH 6.6)	10- 50	0.999	Y=0.004 x+0.002
Phosphate buffer (pH 7.4)	10- 50	0.998	Y=0.020 x-0.007

reduction in sharpness of the XRD peak intensity. This suggests that part of the drug structure may have been converted to the amorphous state.

The XRD pattern of pure Acarbose, SD (AF9) and its physical mixture (AF3) are shown in Figure 5. The XRD scan of pure Acarbose showed intense peaks of crystallinity. The diffractogram of physical mixture was practically a simple superposition of each component; whereas the XRD pattern of prepared SD exhibited a reduction in both number and intensity of peaks compared to the plain Acarbose indicating the decrease in crystallinity or partial amorphization of the drug.

Scanning electron microscopy (SEM)

The SEM of M.HCl in Figure 6 showed the significant effect of solvent evaporation technique compared to unprocessed (Physical mixture) control. In physical mixtures, the Eudragit still exists as individual particles of polymer with M.HCl dispersed in its native crystalline form. SDs in the same polymer drug ratio at 100X magnification, is quite distinct from the physical mixtures, and clearly showed

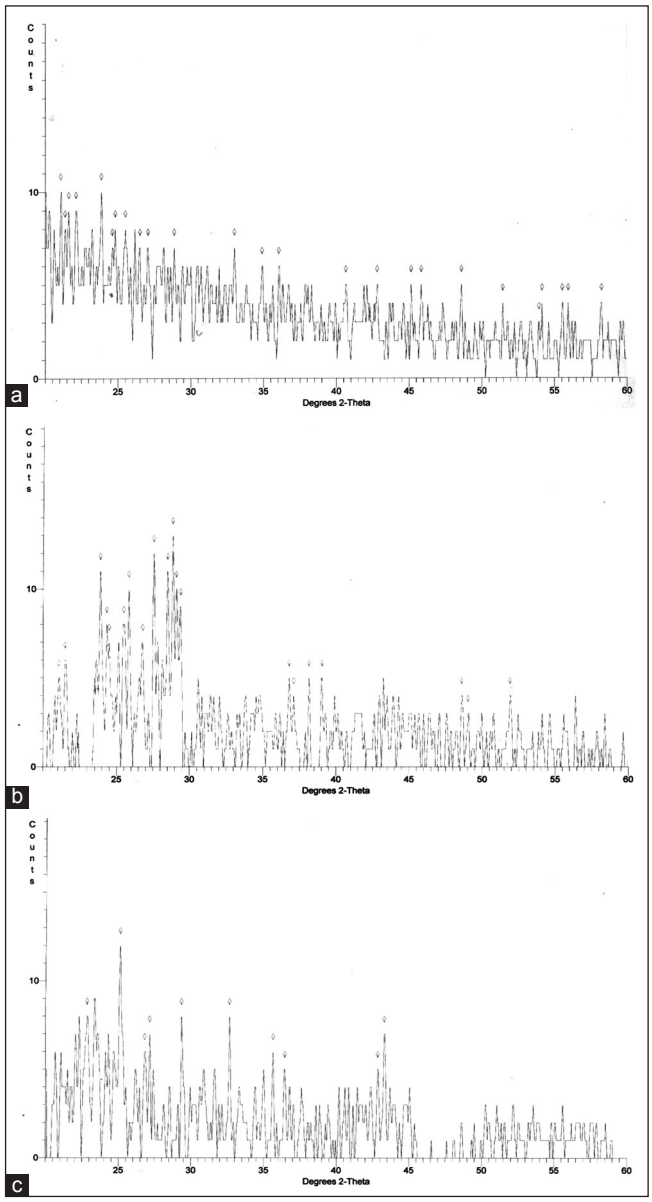

Figure 5: X-ray diffraction patterns of (a) Acarbose (b) AF9 and (c) AF3

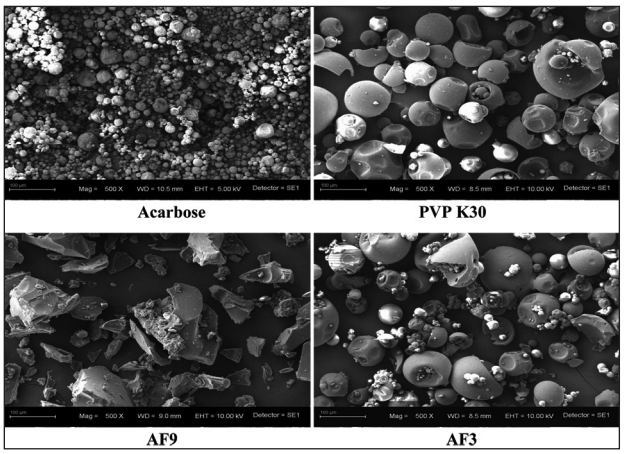

Figure 6: SEM of Acarbose, PVP K30, AF9 and AF3

an interaction between the drug and polymer. As opposed to the physical mixture, these particulates displayed much larger, rougher surfaces, presumably from M.HCl crystals incorporated into the swelled polymer.

SEM micrographs of Acarbose, PVP K30, physical mixtures and SDs at 500X magnification are shown in Figure 7. The pure Acarbose was characterized by crystals of bigger size and regular shape with an apparently smooth surface. In physical mixtures, Acarbose crystals adhered on the surface of polymer (not dispersed in the carrier completely). In contrast, the particles of solid dispersion were fine, porous with rough surface, which might have resulted in the enhanced dissolution rate as compared to pure drug. The photomicrograph of SDs showed that the Acarbose might have dispersed in the carrier.

Differential scanning calorimetry (DSC)

The DSC thermograms of M.HCl and SD are represented in Figure 8. The DSC thermogram of M.HCl alone showed endothermic t_{max} of 224.37 °C, corresponding to the melting point of crystalline form of the drug M.HCl. However, the acrylic resins Eudragit RL-100 and RS 100 does not present any thermal transition in physical mixture, as the melting point did not shift significantly. It can be concluded that no interaction exists between the drug and the polymer. SD formulation MF8 showed that drug peak intensity was reduced further, compared to physical mixture and shifted towards lower temperature. This indicated that M.HCl crystallinity was reduced and the drug might have got converted into the amorphous form.

The DSC thermograms of Acarbose, PVP K30, physical mixture and SD are represented in Figure 9. The DSC thermograms of Acarbose alone showed endothermic t_{max} of 95.6 °C, corresponding to the melting point of crystalline form of the drug Acarbose. The DSC thermogram of PVP K30 showed a sharp endothermic peak at 71.90 °C indicating the melting point of the polymer. The sharp melting point peak of pure Acarbose appeared at 95.6 °C, whereas no such peak was observed in SDs prepared with PVP K30 indicating that Acarbose was molecularly dispersed. However, the peak of polymer in SD was found to be shifted to lower value; 61.19 °C indicating solid-solid phase transition.

Flow properties of solid dispersions

M.HCl SD

Flow properties of ER layer were compared in Table 11. The result of compressibility index (%) ranged from 12.9-24.8, so the powder showed good flow property. The Hausner's ratio ranged from 1.07-1.33. The results of angle of repose ranged from 23.94-42.27. The results of angle of repose indicated excellent flow properties of powder which supported the results found from compressibility index and Hausner's ratio. All these results revealed that the powder possessed satisfactory flow properties and compressibility.

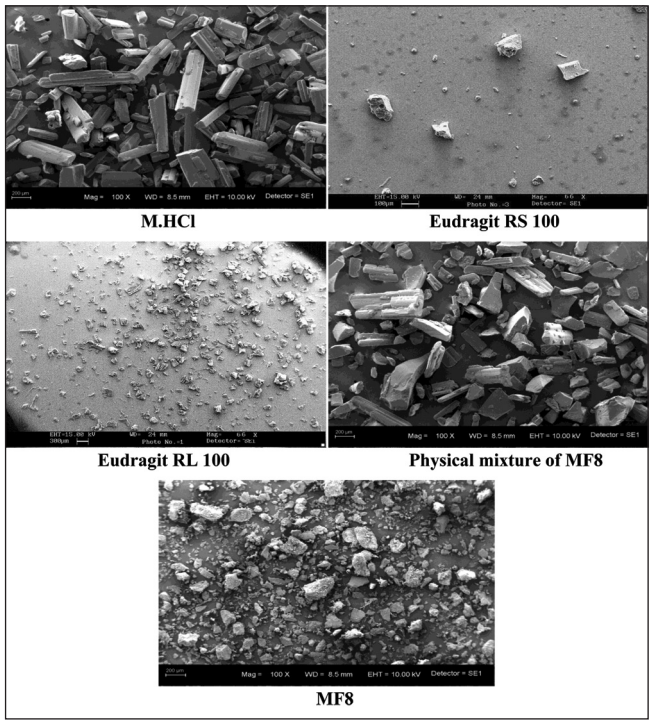

Figure 7: SEM of M.HCl, Eudragit RS 100, Eudragit RL 100, MF8 and physical mixture of MF8

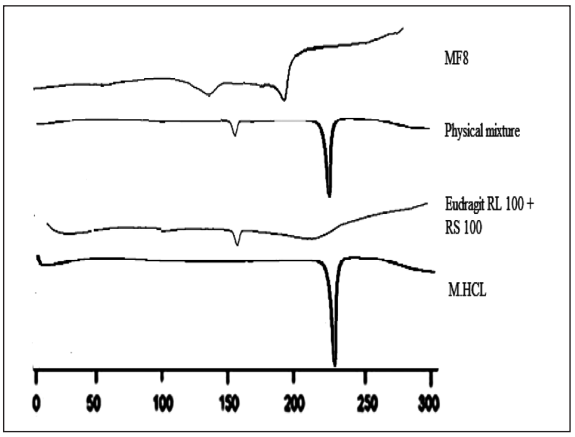

Figure 8: Comparison among DSC thermographs of pure M.HCl, Eudragit RS 100 + RL 100, MF8 and physical mixture of MF8

Acarbose SD

Flow properties of IR layer were compared. Angle of repose, compressibility index and Hasusner's ratio were calculated and were found to be in the range of 19.7- 45, 10.88-31.38 and 1.12-1.45 respectively and is shown in Table 12. All these results revealed that the powder possessed satisfactory flow properties and compressibility.

In-vitro drug release studies of SDs

M.HCl SDs

The results of *in-vitro* drug release studies in phosphate buffer, pH 7.4 for 12 h are depicted in Tables 13 and 14 and Figures 10-12.

Table 11: Flow properties of M.HCl SD

Formulation	Angle of Repose S.D. (degrees)	Hausner's factor S.D.	Compressibility index S.D. (%)
MF1	42.27±2.78	1.27±0.010	21.4±0.71
MF2	33.1±0.33	1.29±0.016	22.73±1.07
MF3	23.96±2.10	1.27±0.010	21.43±0.72
MF4	33.68±0.49	1.30±0.018	23.6±1.30
MF5	36.46±1.23	1.2±0.008	16.66±0.54
MF6	23.94±2.11	1.16±0.018	14.2±1.20
MF7	27.55±1.14	1.33±0.026	24.8±1.62
MF8	39.28±1.98	1.22±0.0026	18.33±0.10
MF9	36.02±1.11	1.25±0.0053	19.99±0.34
MF10	29.74±0.56	1.30±0.018	23.08±1.16
MF11	26.56±1.41	1.15±0.021	13.41±1.41
MF12	29.74±0.56	1.07±0.042	6.68±3.21
MF13	27.55±1.14	1.28±0.013	21.8±0.82
MF14	33.68±0.49	1.24±0.0026	19.78±0.28
MF15	34.21±0.63	1.14±0.024	12.9±1.55

Table 12: Flow properties of Acarbose SD

Formulation	Angle of repose S.D. (degrees)	Hausner's factor S.D.	Compressibility index S.D. (%)
AF1	33.42±0.28	1.21±0.024	17.45±1.60
AF2	26.79±1.71	1.12±0.051	10.88±3.58
AF3	45±3.77	1.26±0.009	20.64±0.64
AF4	38.65±1.86	1.45±0.04	31.38±2.59
AF5	33.68±0.36	1.33±0.012	25.03±0.67
AF6	27.92±1.37	1.30±0.003	25.5±0.21
AF7	28.07±1.32	1.33±0.012	25±0.66
AF8	23.96±2.56	1.34±0.015	25.6±0.85
AF9	36.86±1.32	1.27±0.006	21.79±0.29
AF10	32.61±0.039	1.45±0.048	31.21±2.54
AF11	43.15±3.21	1.31±0.006	23.81±0.31
AF12	19.7±3.85	1.20±0.027	17.18±1.68

Table 13: Dissolution profiles of M.HCl SDs (MF1-MF8)

Time (hrs.)	% Drug release							
	MF1	MF2	MF3	MF4	MF5	MF6	MF7	MF8
0	0	0	0	0	0	0	0	0
0.5	27.4	19.13	6.36	28.94	17.5	12.05	35.84	32.82
1	35.05	30.16	13.27	39.99	25.54	16.35	44.37	40.22
2	45.59	37.55	27.07	48.1	37.25	23.54	48.87	50.34
4	59.4	54.08	42.44	61.91	52.93	36.47	64.9	66.9
6	70.01	64.59	55.84	68.3	65.63	47.11	71.94	77.3
8	79.2	70.57	63.77	76.1	72.23	54.66	79.51	87.81
10	83.72	80.39	70.02	81.9	78.13	66.74	88.49	95.64
12	85.68	83.49	74.86	84.1	80.88	69.35	89.96	98.97

The release behavior depends greatly on the type of polymer used in the formulation. Indeed, there was a difference in the M.HCl release from Eudragit RS 100 or from Eudragit RL 100 or both. M.HCl release from SD prepared with Eudragit RS 100 (MF4, MF5, and MF6) was slower when compared to the SDs prepared with Eudragit RL 100 (MF1, MF2 and MF3). This discrepancy in the release profiles

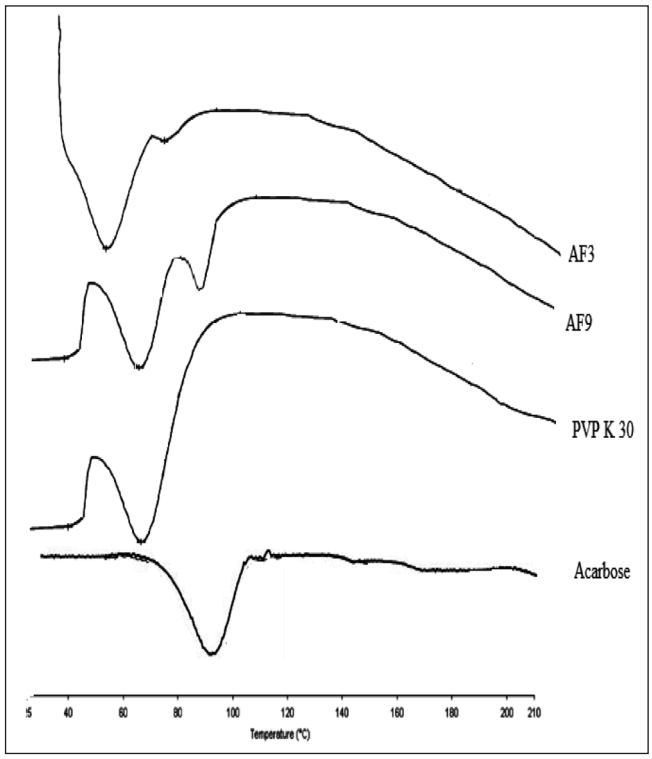

Figure 9: Comparison among DSC thermographs of pure Acarbose, PVP K30, AF9 and AF3

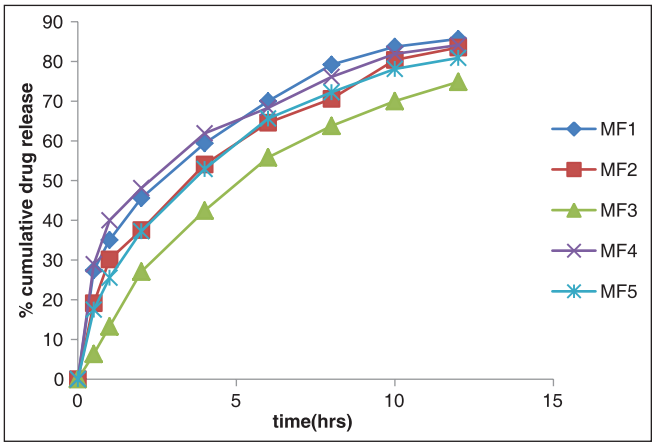

Figure 10: Dissolution profile of M.HCl SDs (MF1- MF5)

Table 14: Dissolution profiles of M.HCl SDs (MF9 - MF15)

Time (hrs.)	% Drug release						
	MF9	MF10	MF11	MF12	MF13	MF14	MF15
0	0	0	0	0	0	0	0
0.5	10.05	28.62	5.36	2.9	29.47	18.9	1.06
1	15.12	38.89	17.44	8.73	34.5	19.44	6.69
2	30.25	43.6	22.14	13.34	43.54	20.088	12.47
4	50.99	48.4	28.24	14.32	47.06	25.02	14.46
6	65.08	56.7	38.32	16.83	49.41	43.2	21.5
8	80.28	62.18	46.44	21.4	52.73	43.6	24.67
10	92.43	66.2	52.02	25.83	55.2	48.41	30.75
12	96.22	69.72	53.1	32.02	63	54.39	34.55

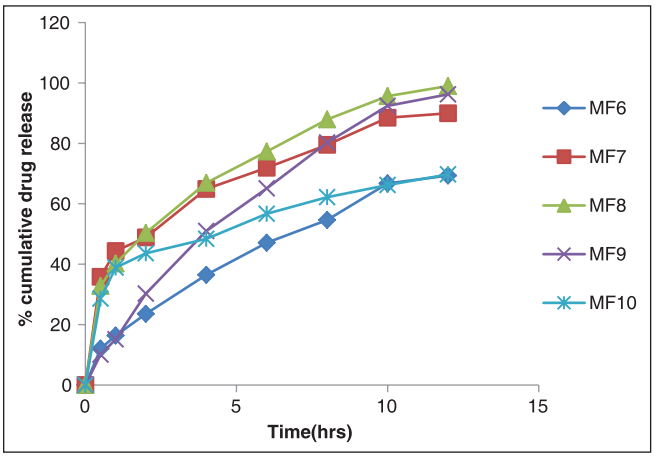

Figure 11: Dissolution profile of M.HCl SDs (MF6- MF10)

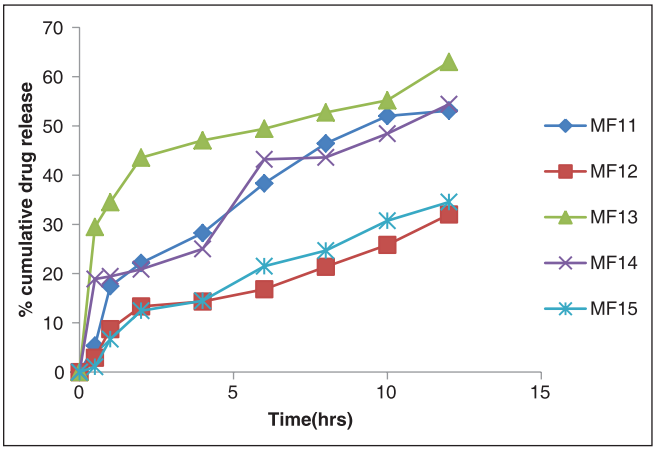

Figure 12: Dissolution profile of M.HCl SDs (MF11- MF15).

was due to the functionality of the quaternary ammonium groups. The Eudragit grades for extended release formulations are based on copolymers of acrylate and methacrylates with quaternary ammonium groups as functional groups as well as ethylacrylate methylmethacrylate copolymers with a neutral ester group. Eudragit RS 100 and RL 100 are water insoluble, nevertheless they are both swellable, that is, permeable to water, representing thus interesting materials for the dispersion of the drugs. This permeability is due to the quaternarium ammonium groups present in their structure. The Eudragit RL-types are highly permeable while the Eudragit RS-types are poorly permeable; therefore, released profiles can be varied by mixing RL and RS types in different ratios. Moreover, the number of hydrophilic quaternary ammonium groups of Eudragit RL 100 was two times higher than that of Eudragit RS 100, resulting in faster drug release from Eudragit RL100 than Eudragit RS 100. However, best results obtained when both Eudragit RS 100 and RL 100 were used in optimum ratios (MF7, MF8 and MF9). Although, MF8 showed best results. Release of M.HCl from SDs prepared by solvent evaporation was better than prepared by physical mixing. It was probably due to the presence of the drug in amorphous state in SDs as compared the physical

mixtures and pure drug, where the drug was present in crystalline state.

Acarbose SDs

Among the solid dispersion and physical mixture of Acarbose formulated with PEG-6000 and PVP K30, AF3 showed highest dissolution rate as comparison to other formulations. The dissolution profiles are shown in Tables 15 and 16 and Figures 13 and 14. From the result, it was clear that, the dissolution rate increases by increasing the carrier concentration. By comparing the dissolution profile of the SDs (Acarbose with PEG- 6000 and PVP K30), it was concluded that the carrier, PVP K30 having ratio of 1:4, revealed the highest improvement in dissolution rate as compared to the PEG-6000. The reason for the lesser release rates with the PEG dispersions in comparison to the PVP SDs might be due to the presence of crystallinity in PEG dispersions and improper wetting of the drug with PEG which resulted in lower release rates. So, PVP K30 was the better carrier among the two selected for preparation of SDs.

Again, all of the SD samples revealed more improved dissolution than their respective physical mixture samples. This observation indicated that the increased dissolution of Acarbose from SDs was due to presence of the drug in amorphous state as compared the physical mixtures and pure drug, where the drug was present in crystalline state.

Evaluation of release kinetics

M.HCl SD

The release kinetics of M.HCl SDs is shown in Table 17. The *in vitro* released profiles of drug from all these formulations could be best expressed by Higuchi's equation as the plots showed highest linearity (r^2 = 0.98 to 0.99). To confirm the diffusion mechanism, the data were fitted into Korsmeyer-Peppas equation. The formulations prepared by solvent evaporation method, showed good linearity (r^2 = 0.953 to 0.999) with slope (n) between 0.215-0.868, which appeared to indicate a coupling of diffusion and erosion mechanisms-so called anomalous diffusion. This indicates, therefore, that drug release from the tablets was controlled more by polymer swelling, followed by the drug diffusion through the swollen polymer, and then by slow erosion of the tablet matrix.

Acarbose SD

The released kinetics of Acarbose SDs is shown in Table 18. The correlation coefficient (r^2) of the slope of these formulations showed an adequate fit to Higuchi model and Peppas as r^2value were in the range of 0.945 - 0.996, 0.991-1 respectively. For zero order r^2 were in the range of 0.880-0.987, 0.926- 0.998 (first order), 0.926-0.995 (Hixon- crowell).

Selection of SDs

Dissolution data shows that MF8 SD displayed higher drug release of 98.97% for 12 h and AF3 SD displayed higher drug release of 97.35% for 120 mins and when dissolution data was subjected to the model independent parameters. It was observed that percentage maximum dissolved of MF8 and AF3 were greater as compared to other formulations. Model dependent parameters revealed that the correlation coefficient of MF8 and AF3 were maximum. On the basis of above mentioned data MF8 and AF3 SDs were selected as optimized formulation.

Table 15: Dissolution profiles of Acarbose SDs (AF1 - AF6)

Time (mins)	Cumulative % drug release					
	AF1	AF2	AF3	AF4	AF5	AF6
0	0	0	0	0	0	0
15	23.62	57.33	59.5	31.81	46.13	47.91
30	34.22	64.2	65.71	38.56	54.6	56.4
45	43.45	71.01	72.93	52.07	63.68	63.1
60	53.1	77.83	78.73	65.58	73.53	72.9
75	65.46	82.64	84.5	72.33	78.3	79.6
90	72.24	86.46	89.07	79.08	82.48	85.75
105	82.11	89.46	93.35	82.46	86.96	91.32
120	84.98	91.46	97.35	82.46	89.96	94.32

Table 16: Dissolution profiles of Acarbose SDs (F7-F12)

Time (mins)	Cumulative % drug release					
	AF7	AF8	AF9	AF10	AF11	AF12
0	0	0	0	0	0	0
15	30.06	42.90	43.25	34.89	37.21	39.76
30	33.63	48.02	48.87	39.03	40.44	51.87
45	47.9	52.20	60.09	46.64	44.49	56.71
60	55.05	57.42	71.31	50.89	52.58	61.56
75	58.62	62.64	74.11	55.13	60.67	66.40
90	62.19	68.45	76.92	59.37	68.76	71.24
105	65.76	73.55	79.72	63.61	72	76.09
120	65.76	73.55	79.72	63.61	72	76.09

Table 17: Release kinetics of M.HCl SDs

Formulations	Zero order	First order	Higuchi	Hixon crowell	Korsmeyer-Peppas	
	r^2	r^2	r^2	r^2	r^2	*N*
MF1	0.918	0.987	0.984	0.972	0.975	0.365
MF2	0.888	0.985	0.986	0.971	0.999	0.53
MF3	0.877	0.990	0.991	0.978	0.986	0.868
MF4	0.918	0.987	0.984	0.972	0.975	0.365
MF5	0.888	0.985	0.986	0.971	0.999	0.53
MF6	0.980	0.993	0.993	0.992	0.995	0.554
MF7	0.952	0.987	0.992	0.988	0.953	0.215
MF8	0.901	0.930	0.996	0.992	0.999	0.315
MF9	0.962	0.960	0.995	0.994	0.991	1.360
MF10	0.938	0.977	0.981	0.969	0.972	0.779
MF11	0.924	0.966	0.978	0.961	0.975	1.116
MF12	0.946	0.951	0.939	0.950	0.973	1.092
MF13	0.904	0.934	0.952	0.922	0.985	0.740
MF14	0.946	0.961	0.925	0.951	0.986	0.793
MF15	0.965	0.979	0.981	0.977	0.960	1.390

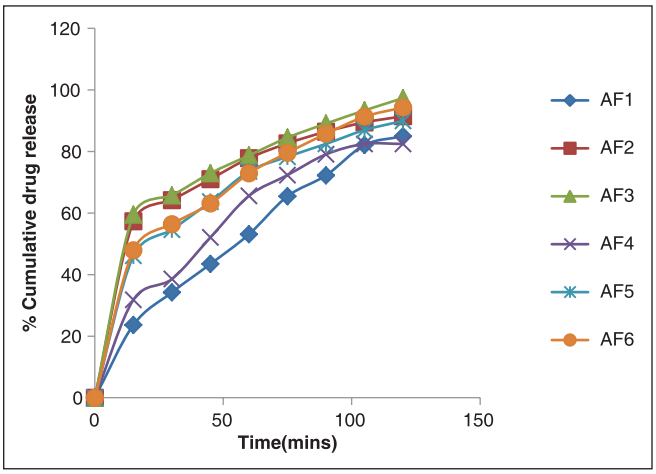

Figure 13: Dissolution profiles of Acarbose SDs (AF1-AF6)

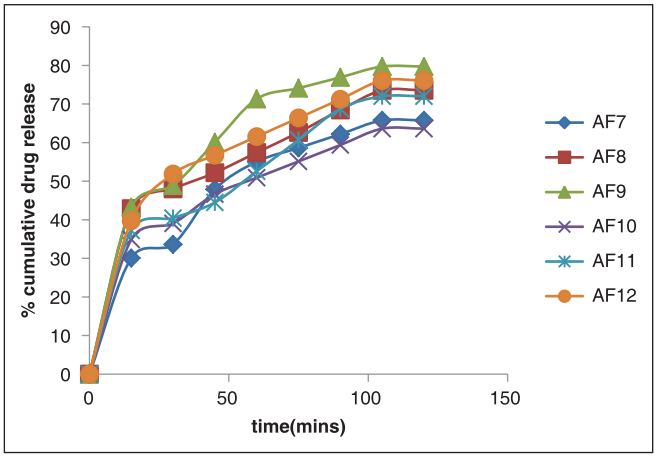

Figure 14: Dissolution profiles of Acarbose SDs (AF7-AF12)

Preparation of Bilayer tablets

Selected SDs (MF8, AF3) were subjected to direct compression along with other excipients. Physical mixtures with the same composition of SDs were tested as a reference.

Evaluation of prepared Bilayer tablets

All the tablets were produced under similar conditions to avoid processing variables. Mass of the Bilayer tablets was 1460 ± 20.20 to1530 ± 20.20 mg, hardness was 12 ± 0.242 to 13 ± 0.334 kg cm^{-2} and thickness was found to be 7.1 ± 0.115 to 7.5 ± 0.115 mm. The percentage friability of all the formulations was found to be 0.46 ± 0.040 to 0.59 ± 0.034% [Table 19]. Values of the hardness test and percent friability indicate good handling properties of the prepared Bilayer tablets.

Drug content, disintegration time and swelling behavior of bilayer tablets

Table 20 summarizes the drug content of prepared Bilayer tablets. Estimation of the drug content in different samples of M.HCl (ER) revealed 94.2-99.6% of expected values. For Acarbose (IR) drug content was found to be 98.1-101.5 % of expected values. The drug content was uniform in all the formulations of Bilayer tablet.

Table 18: Release kinetics of Acarbose SDs

Formulations	Zero order	First order	Higuchi	Hixon crowell	Korsmeyer-Peppas
	r^2	r^2	r^2	r^2	r^2
AF1	0.987	0.976	0.988	0.990	0.991
AF2	0.954	0.998	0.992	0.995	0.999
AF3	0.970	0.926	0.996	0.982	0.998
AF4	0.923	0.973	0.988	0.964	0.996
AF5	0.950	0.984	0.991	0.976	0.998
AF6	0.979	0.969	0.993	0.993	0.995
AF7	0.899	0.944	0.952	0.935	0.997
AF8	0.989	0.980	0.978	0.983	0.998
AF9	0.880	0.942	0.945	0.926	0.998
AF10	0.970	0.981	0.987	0.980	0.998
AF11	0.965	0.959	0.950	0.962	0.996
AF12	0.949	0.984	0.986	0.975	1

Table 19: Post compression parameters of Bilayer tablets

Formulations	Weight S.D.* (mg)	Thickness S.D.* (mm)	Hardness S.D.* (Kg/cm2)	Friability S.D.* (%)
B1	1470±14.4	7.1±0.115	12±0.242	0.46±0.040
B2	1460±20.20	7.5±0.115	12.2±0.127	0.59±0.034
B3	1530±20.20	7.2±0.057	12.5±0.046	0.55±0.011
B4	1520±14.4	7.4±0.057	13±0.334	0.52±0.005

*Each value represents as mean ± S.D. of three determinations

Table 20: Drug content and disintegration time of Bilayer tablets

Formulations	M.HCl		Acarbose	
	Drug content (%)	Disintegration time (mins)	Drug content (%)	Disintegration time (sec)
B1	96	25	101.5	60
B2	94.2	28	98.1	50
B3	98	35	98.4	48
B4	99.6	30	99.7	45

Table 20 also summarizes the disintegration time of both the layers in a Bilayer tablet. M.HCl layer showed a disintegration time of 25-30 mins because of Eudragit polymers while Acarbose layer showed a disintegration time of 45-60 seconds due to carboxymethyl cellulose sodium which was used as a superdisintegrant.

Swelling behavior of Bilayer tablets is shown in Table 21 and Figure 15. Tablets composed of polymeric matrices build a gel layer around the tablet core when they come in contact with water this gel layer governs the drug release. Kinetics of swelling is important because the gel barrier is formed with water penetration. The percentage swelling of all formulations after 12 h was in the range of 22.4-31.90 which may be because of high viscosity and high water retention property Eudragit RS 100 and Eudragit RL 100.

In-vitro drug release of Bilayer tablets

M.HCl

Table 22 and Figure 16 show the drug release after 12 h from different formulations (MB1 to MB4) of Bilayer tablets. Results showed that the MB1 released 84.4%, MB2 released 89.7%, and MB3 released 91.89% while MB4 released 98.55 5% drug in 12 h. It showed that the MB4 was the best formulation.

Acarbose

The concept of superdisintegrant addition method proved to be beneficial in order to lower the disintegration time. The quicker disintegration time may be attributed to faster water uptake by the tablets. When carboxymethyl cellulose sodium was used in the formulations, decrease in disintegration time was noticed. Dissolution profile of the formulations AB1, AB2, AB3 and AB4 are shown in Figure 17 and Table 23. As the concentration of croscarmellose sodium was increased, a decrease in the disintegration time and increase in dissolution of the drug was recorded. From the drug release it was observed that an optimum increase in concentration of croscarmellose sodium increases the drug release. Maximum drug released from AB4 as it contains maximum but optimum amount of croscarmellose sodium.

Table 21: Percentage (%) swelling of Bilayer tablets

Formulations	Swelling (%)
B1	22.4
B2	23.63
B3	30.7
B4	31.90

Table 22: Release of M.HCl from Bilayer Tablets

Time (hrs)	Cumulative % Drug Release			
	MB1	MB2	MB3	MB4
0	0	0	0	0
0.5	33.8	35.1	38.6	44.85
1	42.6	44.8	46.1	52.56
2	48.7	50.1	52.2	59.56
4	60.9	61.5	63.8	71.65
6	68.5	70.1	75.51	80.17
8	73.5	77.9	81.15	88.19
10	81.2	86.5	87.75	94.63
12	84.4	89.7	91.89	98.55

Table 23: Release of Acarbose from Bilayer tablets

Time (mins)	Cumulative % Drug Release			
	AB1	AB2	AB3	AB4
0	0	0	0	0
15	49.3	52.7	55.1	59.1
30	67.4	70.9	72.8	75.5
45	80.3	85.6	86.7	88.2
60	90.5	93.2	96.4	97.5

Release kinetics

M.HCl ER

The kinetics parameters for M.HCl release from Bilayer tablets (MB1-MB4) are shown, in Table 24. The *in-vitro* released profiles of the drug from all the formulations could be best expressed by Higuchi's equation as the plots showed high linearity (r^2 0.994-0.998).

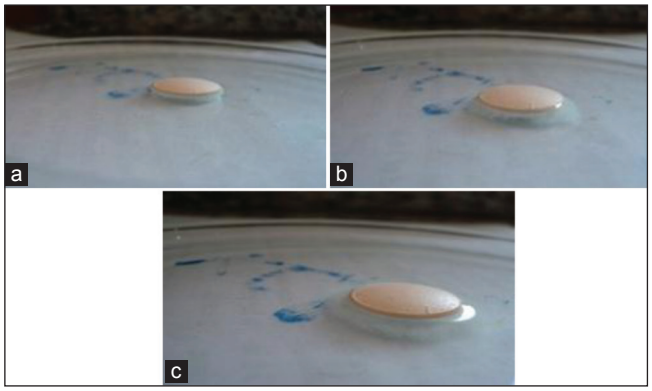

Figure 15: Swelling behavior of Bilayer tablet, B4 (a) 0 mins (b) 6 h (c) 12 h

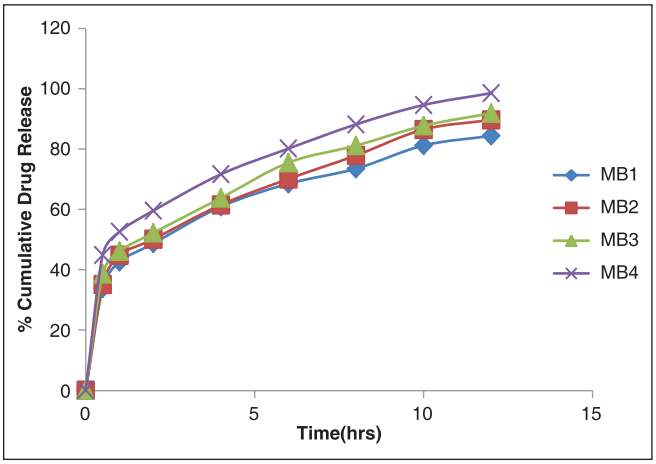

Figure 16: Release of M.HCl from Bilayer tablets

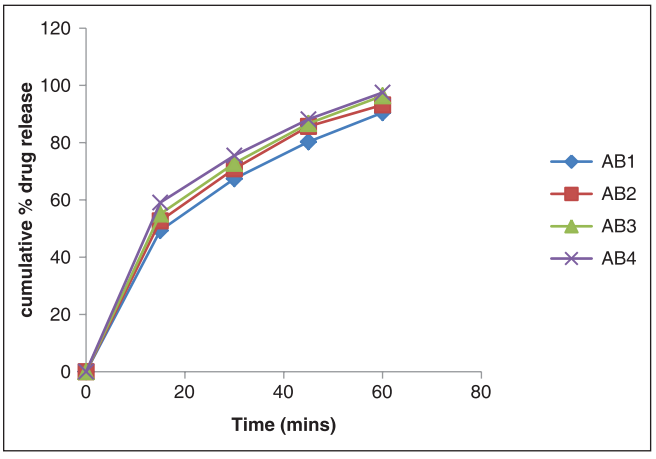

Figure 17: Release of Acarbose from Bilayer tablets

Further to characterize the release mechanism of M.HCl from Bilayer tablets, the dissolution data were subjected to the Korsmeyer-Peppas diffusion model. The 'n' values for all formulations ranged from 0.48 to 0.62, indicating that the release mechanism was non-fickian or anomalous release (0.45 < n < 0.89). The explanation of the release mechanism was that, both Eudragit RS and RL 100 are water insoluble, nevertheless they are both swellable, that is, permeable to water, representing thus interesting materials for the dispersion of the drugs. This permeability was due to the quaternary ammonium groups present in their structure. Therefore, it was postulated that the release mechanism from all the formulations was due to both diffusion and swelling.

Acarbose IR

The kinetics parameters for Acarbose release from Bilayer tablets (AB1 to AB4) are shown, in Table 25. The coefficients of regression were in a range between 0.969-0.984 (Zero order), 0.953-0.991 (First order), 0.990-0.998 (Higuchi) and 0.984-0.998 (Hixon Crowell). The *in-vitro* release profiles of the drug from all the formulations could be best expressed by Higuchi's equation as the plots showed high linearity (r^2 0.990-0.998).

Similarity factor

The similarity factor (f2) method can be used to compare two dissolution profiles. Similarity factor analysis between the prepared tablet and the marketed tablet (Insumet SR, Cadila Pharma) for the release of M.HCl showed an f2 factor of 28.35, 36.42, 47.75 and 50.41 for MB1, MB2, MB3 and MB4 respectively. As shown in Table 26, the f2 factor confirms that the release of M.HCl from MB4 was similar to that of marketed tablet.

For Acarbose, the best formulation i.e. AB4 was taken as reference. All other formulation's dissolution profiles were compared with AB4. Similarity factor analysis between the prepared tablet and the F4 for the release of Acarbose showed an f2 factor of 37.11, 49.54 and 63.18 for AB1, AB2 and AB3 respectively. The f2 factor confirms that the release of Acarbose from the prepared tablets was similar to AB4 [Table 27].

Statistical analysis

The Two-way ANOVA tables for M.HCl ER and Acarbose IR in a Bilayer tablet are shown in Tables 28 and 29 respectively. For M.HCl, when columns were considered, the calculated F value was found to be 3.008 and for rows, the calculated F value was found to be 2.35. F value of 2.39 for columns and 3.04 for rows was needed for significance at 5% level. Moreover, the value of $P > 0.05$, hence they are not statistically significant. In case of Acarbose, when rows were considered, the calculated F value was found to be 3.25 and for columns, the calculated F value was found to

Table 24: Release kinetics of M.HCl from Bilayer tablet

Formulations	Zero order	First order	Higuchi	Hixon crowell	Korsmeyer-Peppas	
	R^2	R^2	R^2	R^2	R^2	*n*
MB1	0.947	0.993	0.994	0.986	0.991	0.59
MB2	0.965	0.990	0.995	0.994	0.932	0.49
MB3	0.959	0.994	0.996	0.996	0.982	0.47
MB4	0.959	0.933	0.998	0.990	0.990	0.50

Table 25: Release kinetics of Acarbose from Bilayer tablet

Formulations	Zero order	First order	Higuchi	Hixon-Crowell
	R^2	R^2	R^2	R^2
AB1	0.983	0.984	0.998	0.998
AB2	0.969	0.991	0.990	0.998
AB3	0.983	0.953	0.997	0.990
AB4	0.984	0.934	0.998	0.984

Table 26: f2 factor results for M.HCl

Time (hrs)	% RELEASE				
	Reference	MB1	MB2	MB3	MB4
0	0	0	0	0	0
0.5	42.6	44.85	38.6	35.1	33.8
1	50	52.56	46.1	44.8	42.6
2	55.2	59.56	52.2	50.1	48.7
4	68.8	71.65	63.8	61.5	60.9
6	76.1	80.17	75.51	70.1	68.5
8	86.1	88.19	81.15	77.9	73.5
10	90.4	94.63	87.75	86.5	81.2
12	95.5	98.55	91.89	89.7	84.4
f2 =		28.35	36.42	47.75	50.41

Table 27: f2 results for Acarbose

Time (mins)	% RELEASE			
	Reference (AB4)	AB1	AB2	AB3
0	0	0	0	0
15	59.1	49.3	52.7	55.1
30	75.5	67.4	70.9	72.8
45	88.2	80.3	85.6	86.7
60	97.5	90.5	93.2	96.4
f2 =		37.11	49.54	63.18

Table 28: Comparative Two–Way ANOVA for dissolution profiles of M.HCl ER in Bilayer tablet

Source of Variation	SS	df	MS	F	*P* value	F crit
Rows	26602.22	8	3325.27	827.32	2.22	2.35
Columns	569.99	3	189.99	47.27	3.17	3.008
Error	96.46	24	4.019			
Total	27268.68	35				

be 3.49. F value of 3.26 and 3.49 were needed for rows and columns respectively for significance at 5% level. Moreover, the value of $P < 0.05$ (for columns). Therefore, alternate hypothesis was accepted (when columns were considered) which indicated that all formulations of Acarbose IR showed significantly different dissolution profiles at different time intervals.

Stability of Bilayer tablets

The stability results of the best Bilayer tablet are presented in Table 30. The results obtained in stability test showed that the appearance, average weight, drug content, hardness and release rate of Bilayer tablet stored at a temperature of 40 ˚C ± 2 ˚C and a relative humidity of 75% was unchanged during three months of accelerating condition storage. It was indicated that SD incorporated in tablet formulation was stable, probably due to the fact that the stable excipients such as, MCC, talc and magnesium stearate were employed in preparation process of tablets; another reason was that the excipients contributed towards protecting the dispersion state of the drugs.

Conclusion

The present research work was carried out to develop a Bi-layer tablet of M.HCl as ER layer and Acarbose as IR layer from their respective SDs.

Eudragit RL 100 and RS 100 were used for the preparation of SD of M.HCl enables the drug release for up to 12 h. Among the different formulations, formulation having Eudragit RL 100 and RS 100 in the ratio of 1:2 (MF8) can be preferred as integrity was maintained. PVP K 30 and PEG 6000 were used for the preparation of SD of Acarbose. Among the different formulations, formulation having Acarbose and PVP K 30 in the ratio of 1:4 (AF3) can be preferred because of maximum drug release and highest correlation coefficient. The analysis by spectral technique (FT-IR) suggested the possibility of hydrogen bonding. The results of DSC, XRD and SEM revealed the reduction in crystallinity of pure drug in SDs as compared to their physical mixtures. The dissolution of M.HCl and Acarbose, which are highly soluble in water, was markedly improved in the SDs using Eudragit RL 100, RS 100 and PVP K30 as carrier respectively.

After the preparation of Bilayer tablet, the result demonstrated that initially burst release was due to carboxymethyl cellulose sodium as superdisintegrant in IR layer and followed by extended release due to combination of polymers such as Eudragit RL 100 and RS 100 in extended release layer. Hence, it concluded that Bi-layer tablets showed an immediate release effect to provide the loading dose of the drug, followed by extended release for 12 h, indicating a promising potential of the M.HCl and Acarbose Bi-layer tablet as an alternative to the conventional dosage form.

Table 29: Comparative two-way ANOVA for dissolution profiles of Acarbose IR in Bilayer tablet

Source of Variation	SS	df	MS	F	*P* value	F crit
Rows	22340.45	4	5585.11	1909.76	1.04	3.25
Columns	116.43	3	38.81	13.27	0.0004	3.49
Error	35.094	12	2.92			
Total	22491.98	19				

Table 30: Stability studies of Bilayer tablets

Tests	1st month results	2nd month results	3rd month results
Appearance	Passes	Passes	Passes
Average weight (mg)	1518	1515	1510
Hardness (Kg/cm^2)	13	12.8	12.5
In-vitro drug release	Passes	Passes	Passes
Drug content (%) (M.HCl, Acarbose)	99.2, 99.1	98, 98.3	97.1, 97.5

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