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Design and development of bilayer tablet for immediate and extended release of Antidiabetic drugs

Vachaspati Dubey[1*], Dr. Gaurav Tiwari[2], Dr. Chandrul Kaushal[1], Dr. Gopal Garg[1]

[1]Department of Pharmacy, Shri Venkateshwara University, Amroha U.P., India
[2]Department of Pharmacy, Pranveer Singh Institute of Technology, Kalpi Road, Bhauti,, Kanpur, U.P., India.

ABSTRACT

The present investigation studied a novel bilayer tablet having extended release system of Metformin HCl (M. HCl) with Eudragit RS 100 and RL 100 and immediate release system of Miglitol with PVP K30 and PEG 6000 in different ratios using solvent evaporation and cogrinding techniques. Solid Dispersions (SDs) were characterized by Fourier-transformed Infrared Spectroscopy (FT-IR), Differential Scanning Calorimetry (DSC), Powder X-Ray Diffractometry (XRD), Scanning Electron Microscopy (SEM) as well as by content uniformity, *in-vitro* dissolution studies and release kinetics. Selected SD system was subjected to Bilayer tablet preparation by direct compression. Compressed tablets were evaluated for drug content, weight variation, friability, hardness, thickness, *and in-vitro* dissolution studies. The progressive disappearance of IR, X-Ray and thermotropic drug signals in SDs and physical mixtures were related to increasing amount of polymer. SEM studies suggested the homogenous dispersion of drug in polymers. FT-IR studies confirmed the formation of hydrogen bonding between drug and polymer. All tablet formulations showed compliance with pharmacopoeial standards. The formulations gave an initial burst effect to provide the loading dose of the drug followed by extended release for 12 hrs (Higuchi model via a non-fickian diffusion controlled release mechanism). Stability studies conducted for optimized formulation did not show any change in physical properties, drug content, and *in-vitro* drug release.

Keywords: - Metformin HCl, Miglitol, Eudragit RS 100, RL 100, PVP K30, PEG 6000, Solid Dispersions, Bilayer Tablets.

1. INTRODUCTION

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 primarily by decreasing

***Corresponding Author:**
Vachaspati Dubey
Department of Pharmacy, Shri Venkateshwara University, Amroha U.P., India
E.Mail: vpdubey7@gmail.com, drgauravtiwari81@gmail.com
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hepatic glucose output and has a comparatively lesser effect increasing insulin sensitivity. Isotope studies suggest 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 fasting glucose levels, thereby reducing hemoglobin A1c. The degree of clinical effect varies in individual patients, but most 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 patients.[1]

Miglitol belongs to the class of alpha-glucosidase inhibitors. It inhibits intestinal enzymes that digest carbohydrate, thereby reducing carbohydrate digestion after meals. This lowers postprandial glucose elevation in diabetics. Miglitol in combination with M. HCl has the potential to delay diabetes complications through improvement of metabolic control. There was also a favorable effect on fasting blood glucose levels. Reduced glucose toxicity through decreasing postprandial blood glucose elevations and a beneficial effect of the increased late rise in glucagon-like peptide on reducing fasting blood glucose are possible mechanisms for this effect. Miglitol 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 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 literature for use in improvement of bioavailability and controlled delivery of drugs.[2]

The layered tablet concept has been utilized to develop 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 withsingle 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 Miglitol 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.

2. MATERIALS AND METHODS

2.1. Materials

M. HCl was supplied by Ipca Laboratories. Dehradoon. Miglitol (Avicel PH101) was obtained from Windlas Biotech, Dehradoon. Eudragit RS100 (RS100) and Eudragit RLPO (RLPO) were gifted by Rohm Pharma, Germany. Potassium permanganate, Caboxymethyl cellulose sodium, Magnesium

stearate, PEG 6000 and PVP K30 were generously gifted by S.D Fine Chem Limited, Mumbai. Other chemicals were of analytical grade. Double distilled water was used throughout the studies.

2.2. Preparation of M. HCl and Miglitol SDs

2.2.1. Physical mixing

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 (Table 1), 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.

Physical mixtures of Miglitol were obtained by blending Miglitol and two carriers (PEG 6000, PVP K 30) in different ratios (Table 2) 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 [12].

2.2.2. Solvent evaporation

The required amount of drug and the carriers in different ratios (Table 1 and 2) were dissolved in sufficient volume of ethanol with continuous stirring. The solvent was then completely evaporated at 45ºC with continuous stirring to obtain dry mass. The dried mass was pulverized, passed through 44 mesh sieve and stored in desiccator until used for further studies.

2.3. Drug content study

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 and 209.4nm respectively for M. HCl and Miglitol. Drug content was calculated using the calibration curve [12].

2.4. Characterization of SDs

2.4.1. 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 10^0C to 60^0C, at an angular speed of 1^0 (2θ) per minute.

2.4.2. FTIR SPECTROSCOPY (FTIR)

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.

2.4.3. 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 gold sputter model in a high vacuum evaporator. Samples were then observed with scanning electron microscopy.

2.4.4. 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 70^0C to 250^0C at a rate of 10^0C/minute in nitrogen atmosphere.

2.5. Evaluation of granules

The granules were evaluated for angle of repose, loose bulk density, tapped bulk density, compressibility index and Hausners index [13-15].

2.6. Preparation of bilayer tablets

Optimized formulations of M. HCl ER SD (MF8) and Miglitol IR SD (MGF3) were selected and final Bilayer tablets were prepared according to the following formula (Table 3).

Final Bilayer tablets were compressed as one layer only for M. HCl and second layer for Miglitol 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 Miglitol powder. In this, M. HCl powder were introduced first into the die cavity and a slight pre compression was made so that the layer was uniformly distributed, after that Miglitol powder was added and a final compression was made [1,16].

2.7. Evaluation of tablets

The prepared matrix tablets were evaluated for hardness, weight variation, thickness, friability and drug content. Hardness of the tablets was tested using a Strong- Cobb hardness tester (Tab-machine, Mumbai, India). Friability of the tablets was determined in a Roche friabilator (Campbell Electronics, Mumbai, India). The thickness of the tablets was measured by vernier caliper. Weight variation test was performed according to the official method [17].

2.8. Swelling studies

The swelling properties and the erosion characteristics of tablets were evaluated by determination of the percentage of hydration and matrix erosion or dissolution (DS). The percent values were calculated according to the following equations:

$$\% \text{ Hydration} = \frac{(W2 - W1)}{W2} * 100$$

$$DS = \frac{W1 - W3}{W1} * 100$$

Each tablet was weighed (W1) and immersed in a simulated salivary fluid11 at pH 6.75 for predetermined times (0, 6 and 12 hours). After immersion, excess surface water was removed from the tablets using filter paper and weighed (W2). The swollen tablets were dried at 60^0C for 24 hours in an oven and kept in a desiccator for 48 hours prior to reweighing (W3). This experiment was performed in triplicate [18].

2.9. Determination of *in-vitro* drug release of SDs and tablets

Dissolution tests for SDs 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 7.4) was maintained at 37±0.5^{0}C and stirred at 100 rpm. The release of Bilayer tablet was determined using USP dissolution apparatus II at 50 rpm. At predetermined intervals, 5mL of sample 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 209.4nm for Miglitol. The tests were performed three times to check repeatability [8].

2.10. Drug release kinetics

In model-dependent approaches, release data were fitted to five kinetic models including the zero-order (Equation 1), first order (Equation 2), Higuchi matrix (Equation 3), Peppas–Korsmeyer (Equation 4), and Hixson–Crowell (Equation 5) release equations to find the equation with the best fit using PCP Disso v3 software, Pune, India [19].

R = k1t ---------- (1)

logUR = k2t / 2:303 ---------- (2)

R = k3_t ---------- (3)

logR = log k4 + n log t ---------- (4)

(UR) 1/3 = K5 t ---------- (5)

2.11. 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^{o}C and 75% RH and 37^{o}C in stability chamber. At the end of studies, tablets were evaluated for physical properties, *in- vitro* drug release and drug content [20].

3. RESULTS AND DISCUSSION

3.1. Characterization of SDs

Physical mixtures with the same composition of SDs were tested as a reference for FTIR. In fact observations indicated that most interaction between M. HCl and Eudragit, Miglitol 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 Miglitol. This showed that there was no interaction between the drug and polymers. However in comparison with their physical mixtures, M. HCl and Miglitol both gave a broad band in their respective SDs. This result suggested the presence of intermolecular hydrogen bonding between M. HCl and Eudragit, Miglitol and PVP K30 in SDs (Figure 1 and 2). XRD spectra of M. HCl SD ie. MF8 and its physical mixture showed in Figure 3. 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 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 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 Miglitol, SD (MGF9) and its physical mixture (MGF3) showed in Figure 4. The XRD scan of pure Miglitol 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 Miglitol indicating the decrease in crystallinity or partial amorphization of the drug. The SEM of M. HCl in Figure 5 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 an interaction between 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 Miglitol, PVP K30, physical mixtures and SDs at 500X magnification showed in Figure 6. The pure Miglitol was characterized by crystals of bigger size and regular shape with an apparently smooth surface. In physical mixtures, Miglitol 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 Miglitol might have dispersed in the carrier. The DSC thermograms of M. HCl and SD are represented in Figure 7. 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 Miglitol, PVP K30, physical mixture and SD are represented in Figure 8. The DSC thermograms of Miglitol alone showed endothermic t_{max} of 95.6°C, corresponding to the melting point of crystalline form of the drug Miglitol. The DSC thermogram of PVP K30 showed a sharp endothermic peak at 71.90°C indicating melting point of the polymer. The sharp melting point peak of pure Miglitol appeared at

95.6°C, whereas no such peak was observed in SDs prepared with PVP K30 indicating that Miglitol 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.

3.2. Flow properties of solid dispersions

The result of compressibility index (%) ranged from 12.9-24.8, revealed 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.

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. All these results revealed that the powder possessed satisfactory flow properties and compressibility.

3.3. Preparation and evaluation of bilayer tablets

Selected SDs (MF8, MGF3) were subjected to direct compression along with other excipients. Physical mixtures with the same composition of SDs were tested as a reference. 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 4). Values of the hardness test and percent friability indicate good handling properties of the prepared Bilayer tablets.

3.4. Drug content, disintegration time and swelling behavior of bilayer tablets

Table 5 summarizes the drug content of prepared Bilayer tablets. Estimation of drug

content in different samples of M. HCl (ER) revealed 94.2- 99.6% of expected values. For Miglitol (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 5 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 Miglitol layer showed a disintegration time of 45-60 sec due to Carboxymethyl cellulose sodium which was used as a superdisintegrant.

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 % swelling of all formulations after 12 hours was in the range of 22.4-31.90 (Table 5 and Figure 9) which may be because of high viscosity and high water retention property Eudragit RS 100 and Eudragit RL 100.

3.5. *In-vitro* drug release studies of SDs

The results of *in-vitro* drug release studies in phosphate buffer, pH 7.4 for 12 hrs are depicted in Figure 10. 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 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 drugs. This permeability is due to the quaternary ammonium groups present in their structure. The Eudragit RL-types are highly permeable while the Eudragit RS-types are poorly permeable; therefore, release 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, formulation 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 drug in amorphous state in SDs as compared the physical mixtures and pure drug, where drug was present in crystalline state.

Among the solid dispersion and physical mixture of Miglitol formulated with PEG-6000 and PVP K30, MGF3 showed highest dissolution rate as comparison to other formulations. The dissolution profiles showed in Figure 11. From the result, it was clear that, the dissolution rate increases by increasing the carrier concentration. By comparing the dissolution profile of the SDs (Miglitol with PEG- 6000 & PVP K30), it was concluded that the carrier, PVP K30 having ratio of 1:4, revealed 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 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 Miglitol from SDs was due to presence of drug in amorphous state as compared the physical mixtures and pure drug, where drug was present in crystalline state.

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 hrs. It showed that the MB4 was the best formulation (Figure 12). 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 MGB1, MGB2, MGB3 and MGB4 showed in Figure 13. As the concentration of Croscarmellose sodium was increased, a decrease in the disintegration time and increase in dissolution of 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 MGB4 as it contains maximum but optimum amount of Croscarmellose sodium.

3.6. Evaluation of release kinetics

The *in vitro* release 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 drug diffusion through the swollen polymer, and then by slow erosion of the tablet matrix. The release kinetics of

Miglitol SDs revealed 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).

The *in-vitro* release profiles of M. HCl from all the formulations could be best expressed by Higuchi's equation as the plots showed high linearity (r^2 0.994-0.998). 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 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.

The kinetics parameters for Miglitol release from Bilayer tablets (MGB1 to MGB4) revealed coefficients of regression 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 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).

3.7. Statistical analysis

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

Miglitol, when rows were considered, the calculated F value was found to be 3.25 and for columns, the calculated F value was found to 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 Miglitol IR showed significantly different dissolution profiles at different time intervals.

3.8. Stability of bilayer tablets

The stability results of the best Bilayer tablet are presented in Table 6. 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 $40^0C \pm 2^0C$ 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.

4. CONCLUSION

The present research work was carried out to develop a Bilayer tablet of M. HCl as ER layer and Miglitol as IR layer from their respective SDs. Eudragit RL 100 and RS 100 were used for the preparation of SD of M. HCl enables drug release for upto 12 hrs. 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 Miglitol. Among the different formulations, formulation having Miglitol and PVP K 30 in the ratio of 1:4 (MGF3) 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 Miglitol, 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 hrs, indicating a promising potential of the M. HCl and Miglitol Bilayer tablet as an alternative to the conventional dosage form.

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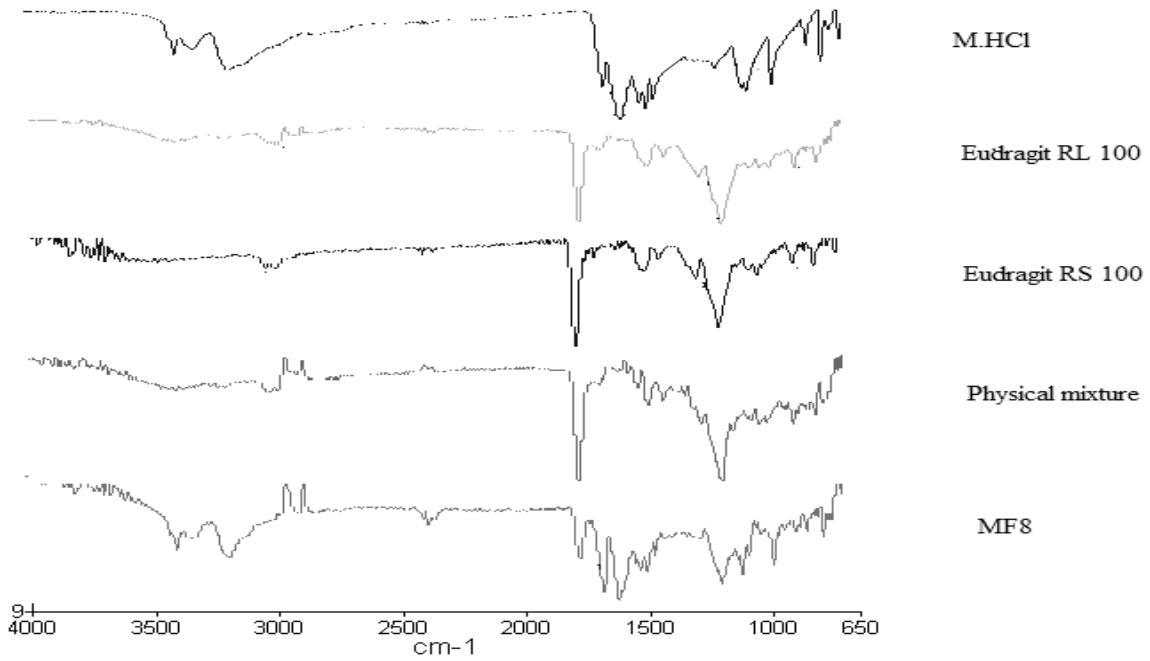


Fig 1: FT-IR Spectrum of M.HCl, Eudragit RL100, Eudragit RS 100, Physical mixture, MF8

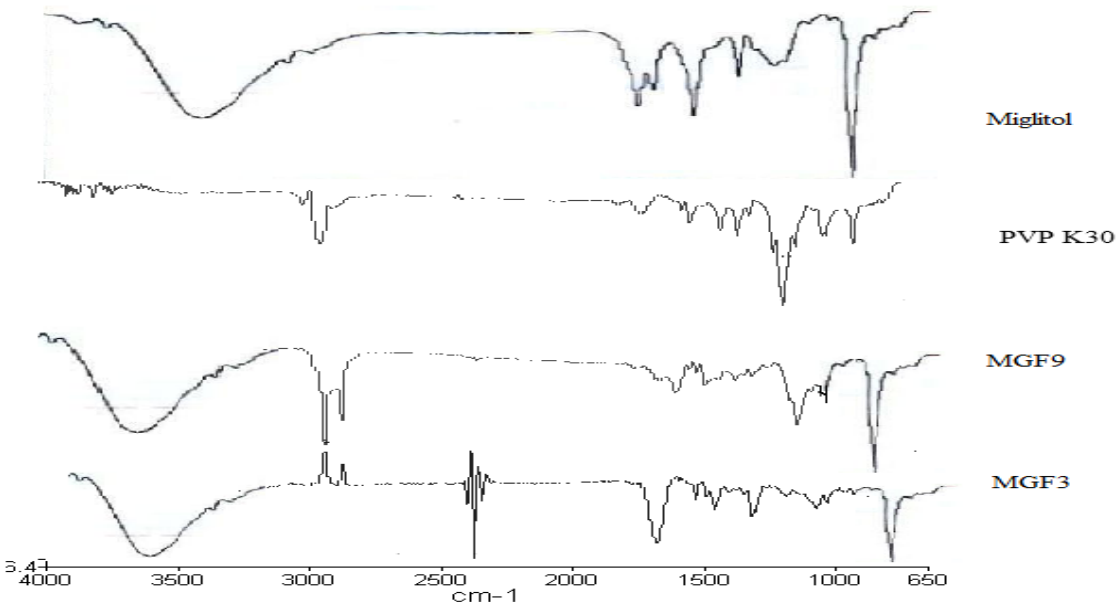


Fig 2: FT-IR Spectrum of Miglitol, PVP K30, MGF9 and MGF3

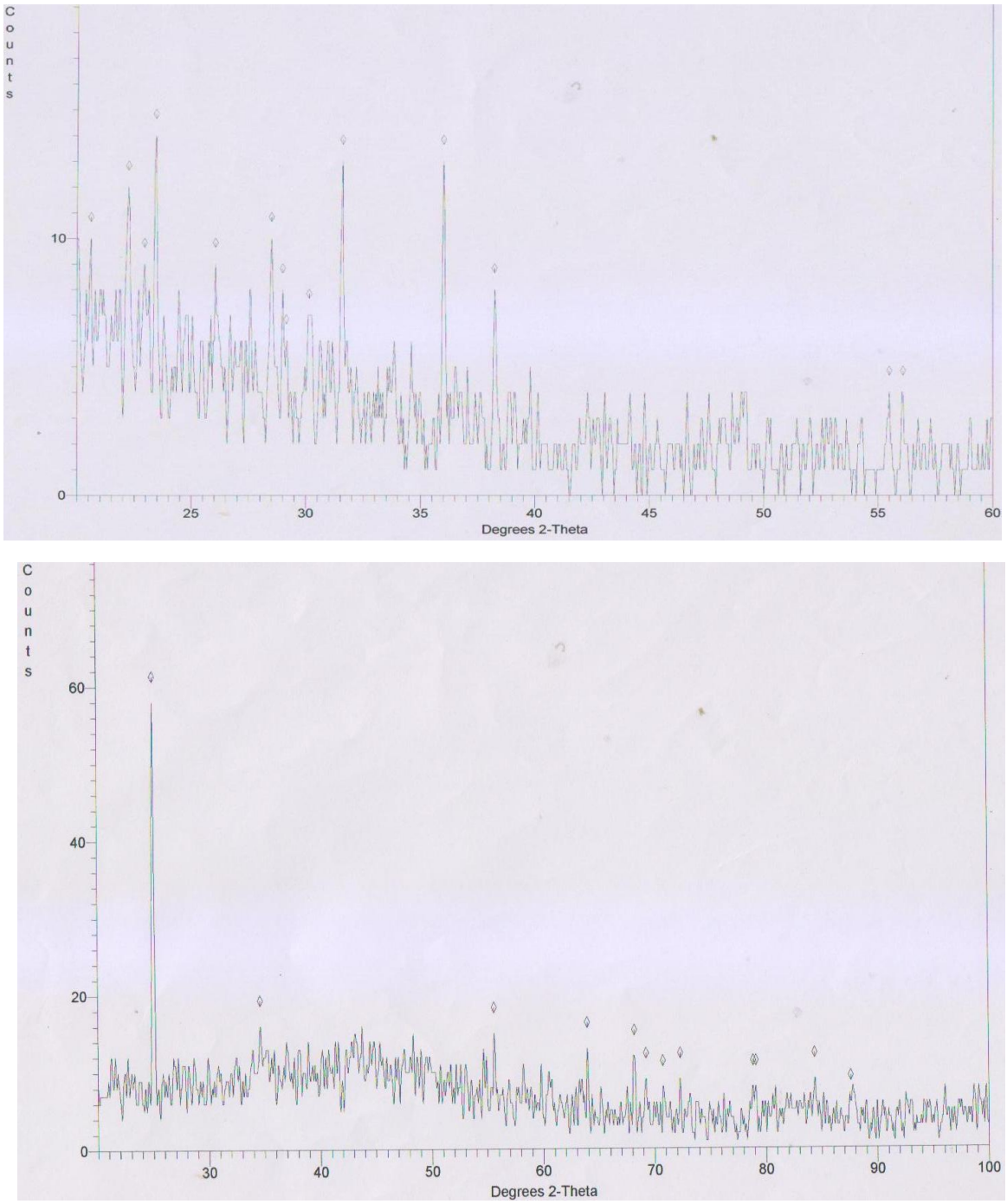


Fig 3 X-Ray diffraction patterns of Physical mixture (A) and MF8 (B)

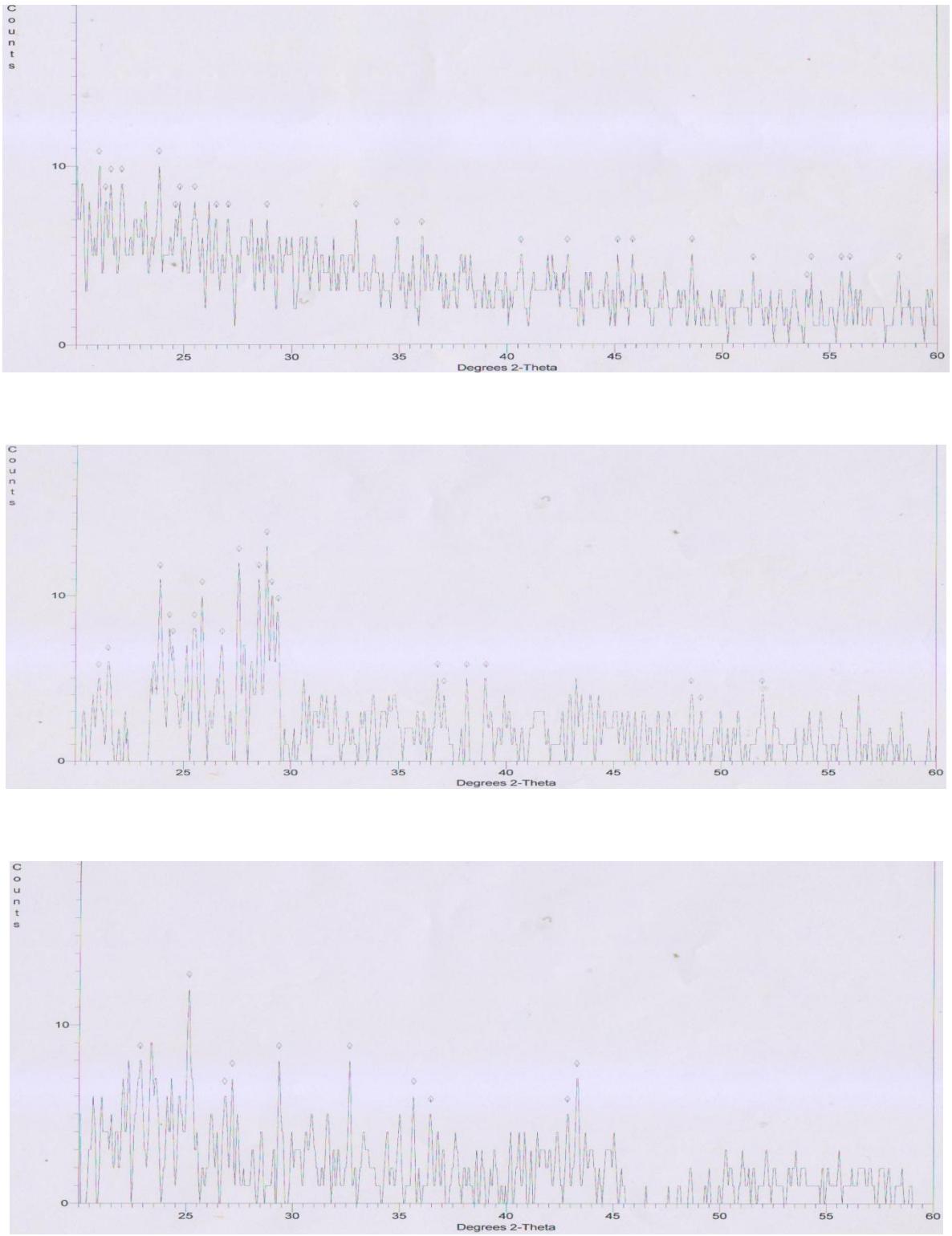
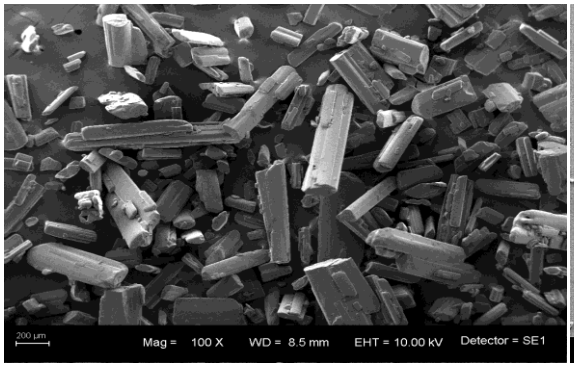
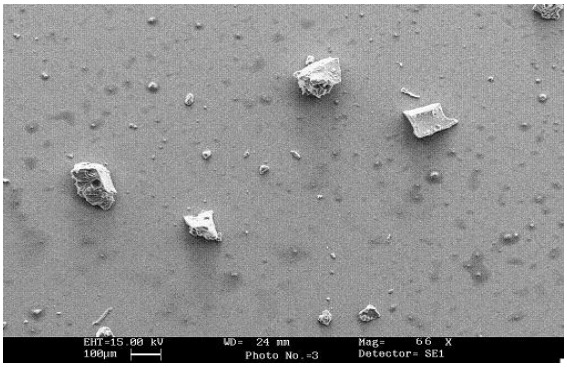


Fig 4 X-Ray diffraction patterns of (A) Miglitol (B) MGF9 and (C) MGF3



M.HCl



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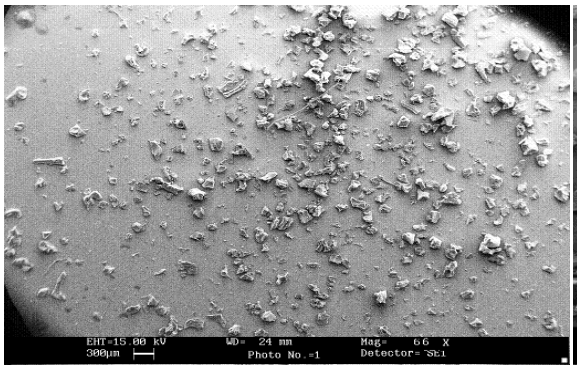

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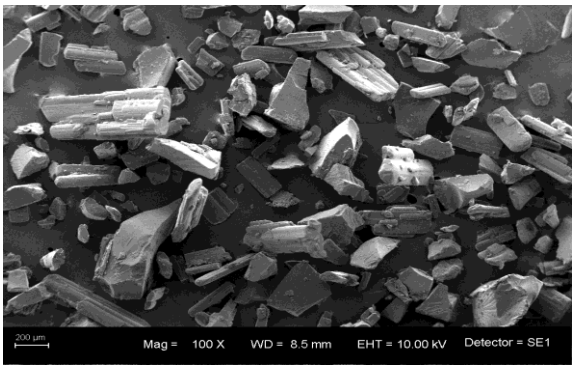
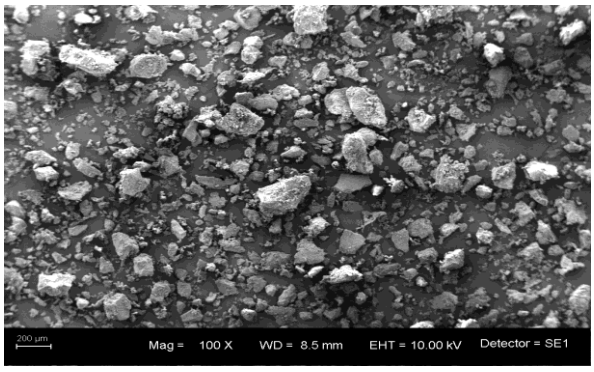
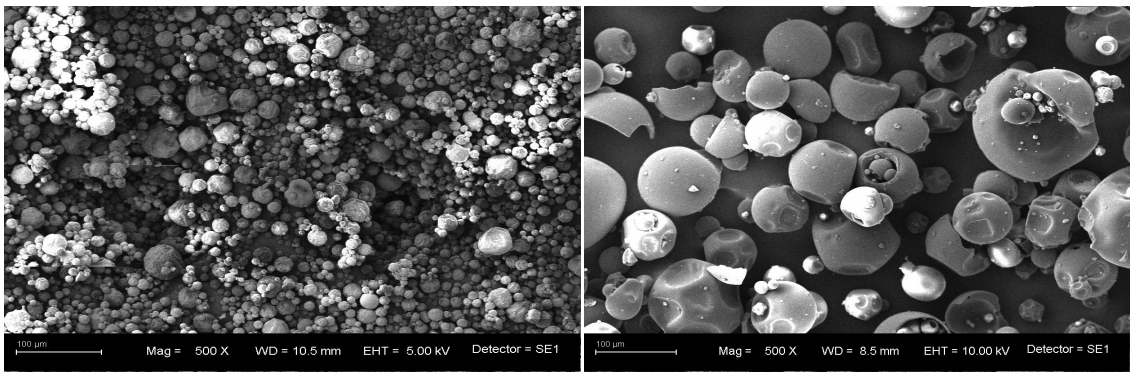


Physical mixture

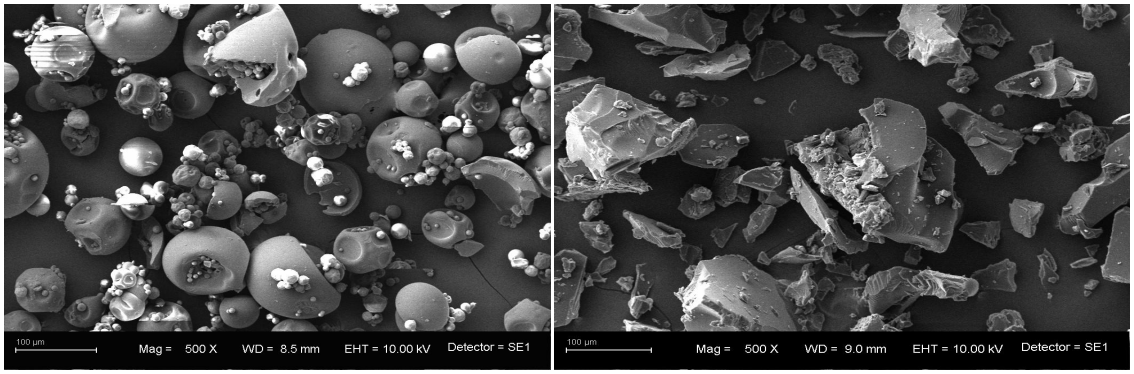


MF8

Fig 5: SEM of M.HCl, Eudragit RS 100, Eudragit RL 100, MF8 and Physical mixture



Miglitol **PVP K30**



MGF9 **MGF3**

Fig 6: SEM of Miglitol, PVP K30, MGF9 and MGF3

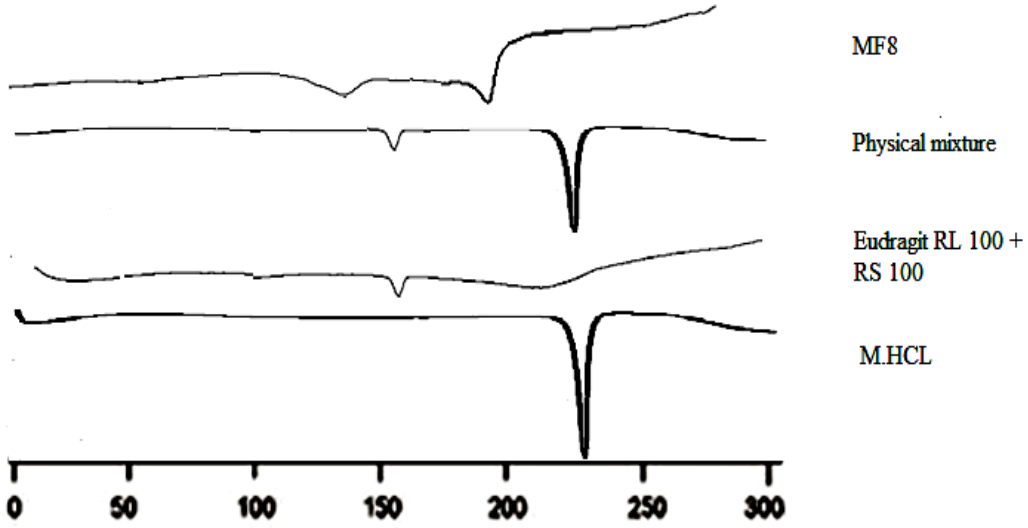


Fig 7: Comparison among DSC thermographs of pure M.HCl, Eudragit RS 100 + RL 100, MF8 and Physical mixture of MF8

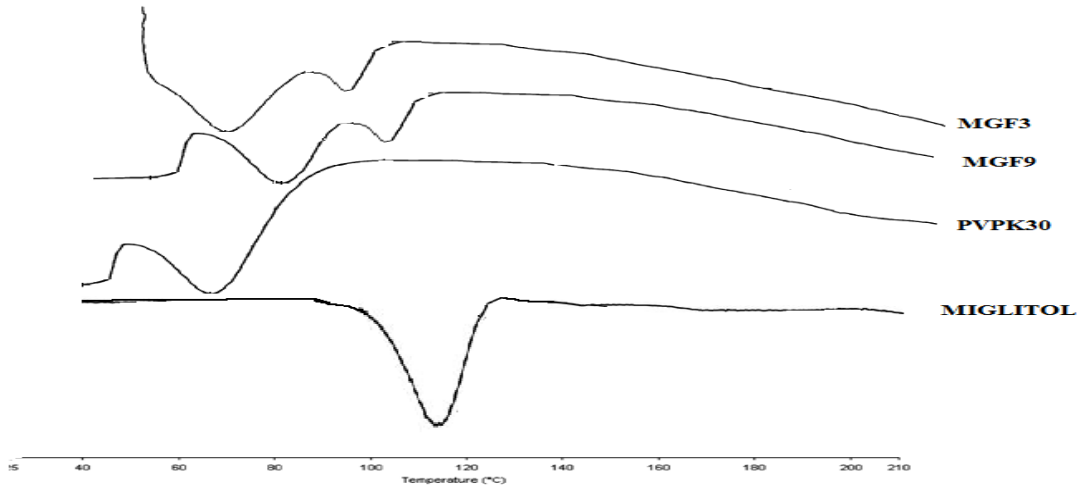


Fig 8: Comparison among DSC thermographs of pure Miglitol, PVP K30, MGF9 and MGF3

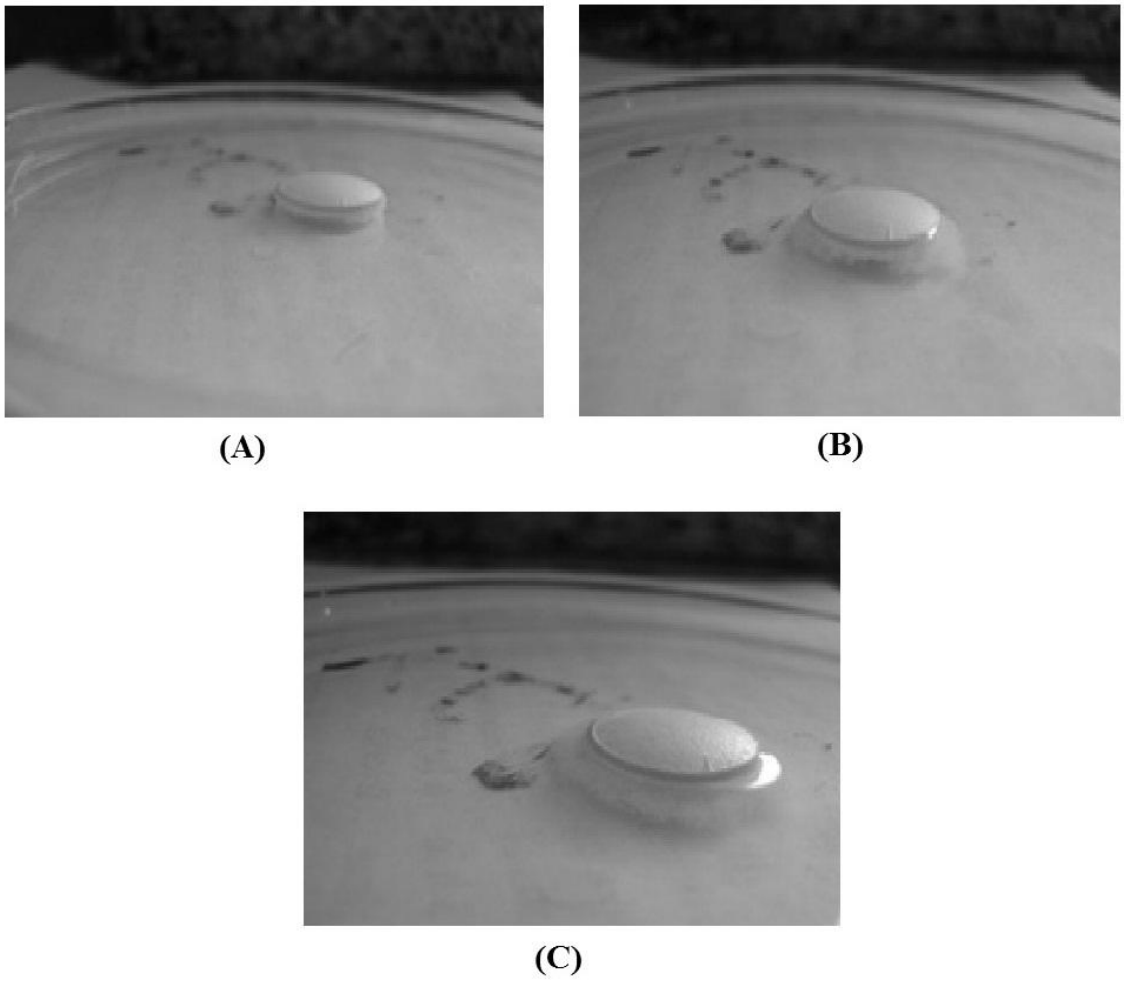


Fig. 9: Swelling Behavior of Bilayer Tablet, B4 (A) 0 mins (B) 6 hr (C) 12 hr

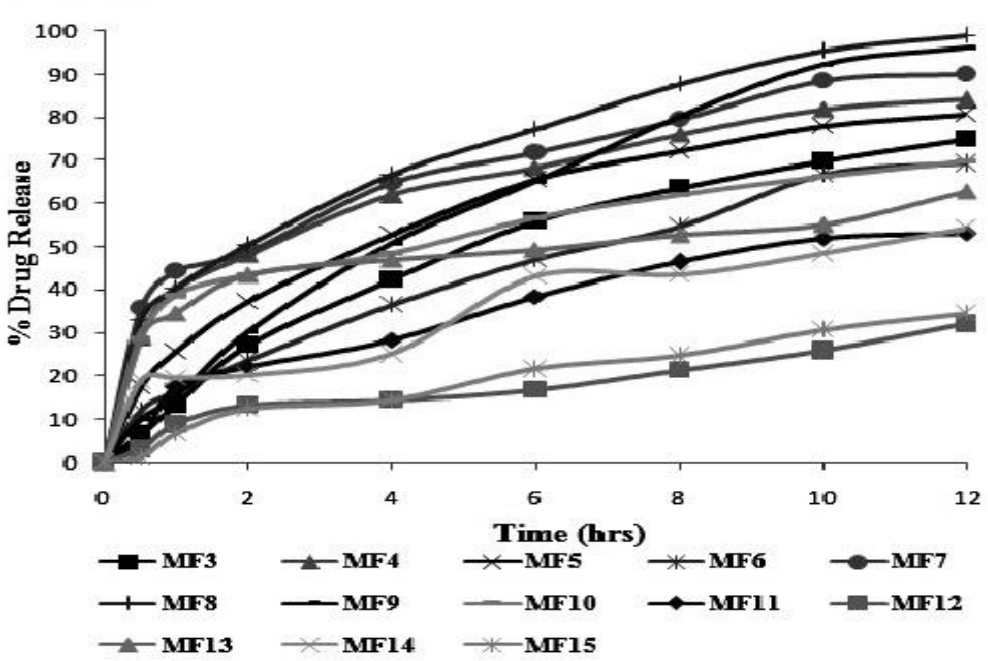


Fig 10: Dissolution profile of M.HCl SDs (MF11- MF15)

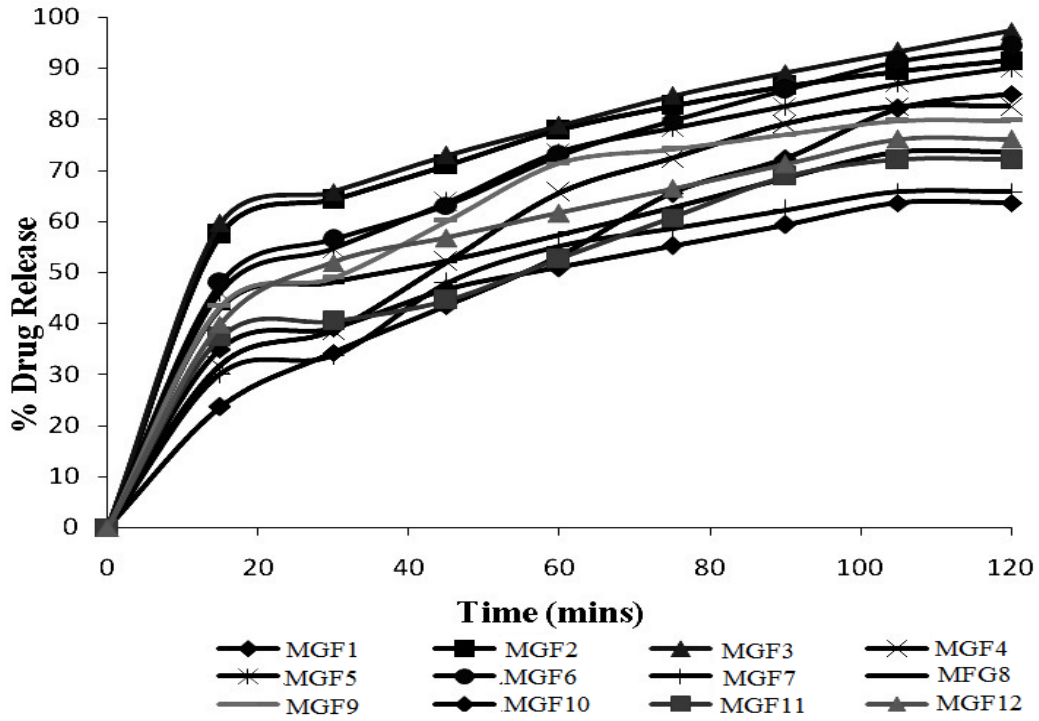


Fig 11 Dissolution profiles of Miglitol SDs (MGF1-MGF12)

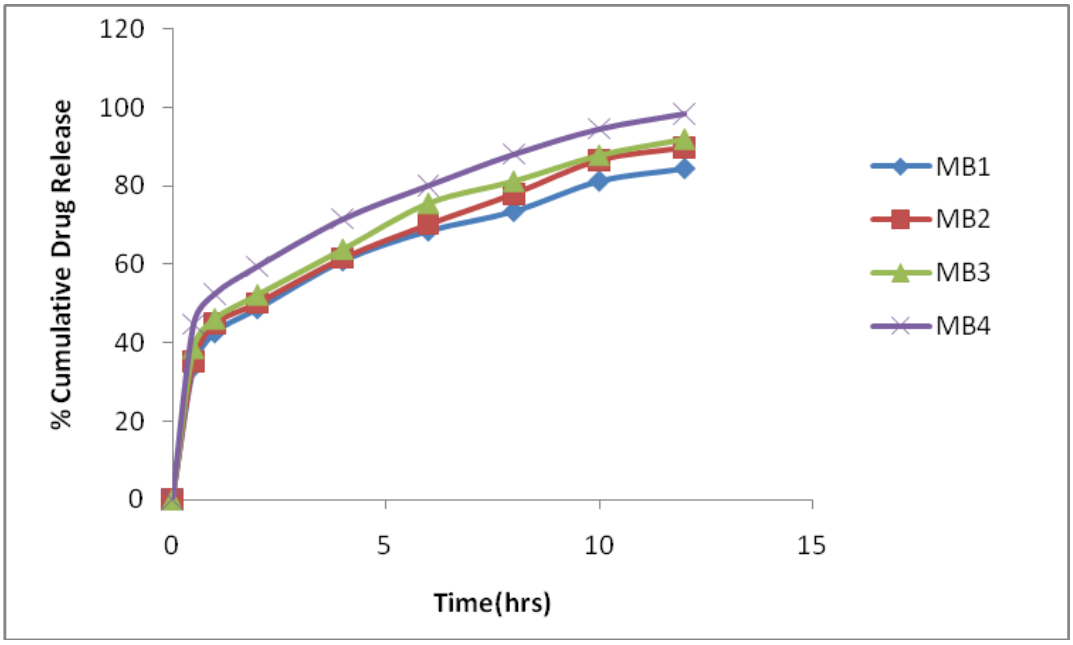


Fig 12: Release of M.HCl from Bilayer Tablets

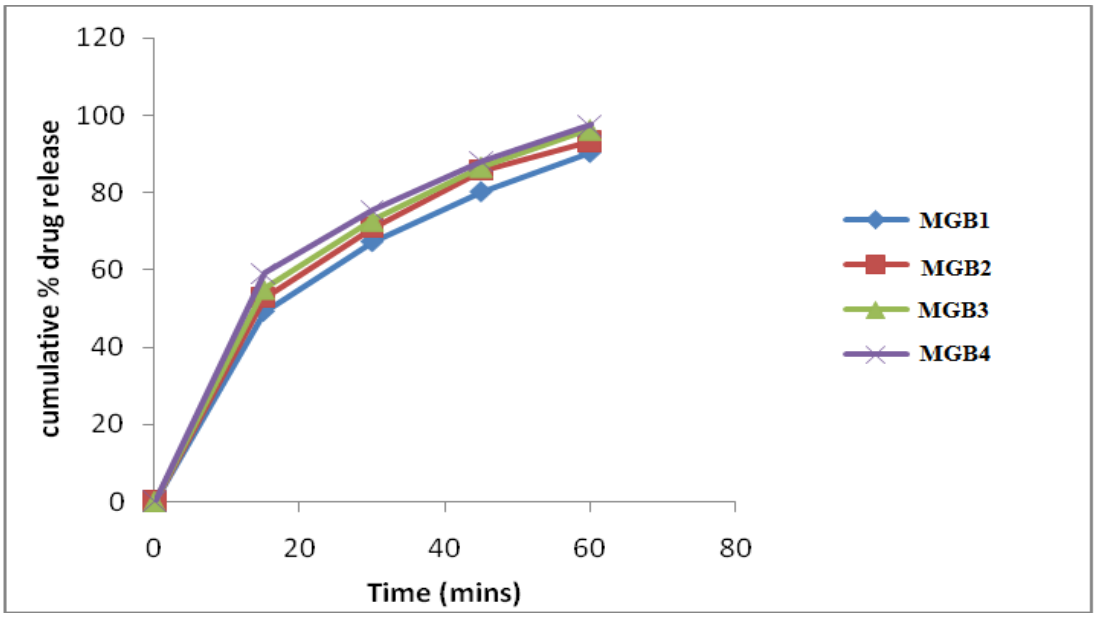


Fig.13: Release of Miglitol from Bilayer Tablets

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	EudragitRL100,	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 Miglitol

Formulation Code	Carrier	Drug : Carrier	Method
MGF1	PVP K 30	1:1	Solvent Evaporation
MGF2		1:2	
MGF3		1:4	
MGF4	PEG 6000	1:1	Solvent Evaporation
MGF5		1:2	
MGF6		1:4	
MGF7	PVP K 30	1:1	Physical Mixture
MGF8		1:2	
MGF9		1:4	
MGF10	PEG 6000	1:1	Physical Mixture
MGF11		1:2	
MGF12		1:4	

Table.3. Composition of bilayer tablets

Formulation Code	Solid Dispersion eq. to drug (mg)	MCC (mg)	Magnesium Stearate (mg)	Talc (mg)	Carboxymethyl cellulose sodium (mg)	Sunset Yellow (mg)
MB1	854	445	2	5	-	0.5
MGB1	40	167	2	5	4	0.5
MGB2	30	168	2	5	6	0.5
MGB3	30	159	2	5	8	-
MGB4	30	156	2	5	10	-

Table 4. Post compression parameters of Bilayer Tablets

Formulations	Weight± SD* (mg)	Thickness± SD* (mm)	Hardness± SD* (Kg/cm2)	Friability± SD* (%)
B1	1478 ± 15.4	7.1 ± 0.115	12 ± 0.242	0.47 ± 0.040
B2	1466 ± 25.20	7.5 ± 0.115	12.2 ± 0.127	0.59 ± 0.034
B3	1538 ± 22.20	7.2 ± 0.057	12.5 ± 0.046	0.56 ± 0.011
B4	1528 ± 15.4	7.4 ± 0.057	13 ± 0.334	0.52 ± 0.005

*****Each value represents as mean ± SD of three determinations

Table 5. Drug content and disintegration time of Bilayer tablets

Formulations	M.HCl		Miglitol		Swelling (%)
	Drug content (%)	Disintegration time (mins)	Drug content (%)	Disintegration time (secs)	
B1	99	25	102.5	56	23.4
B2	94.2	28	98.1	50	23.63
B3	98	35	98.4	56	30.7
B4	99.5	30	97.7	40	32.90

Table 6. Stability studies of Bilayer tablets

S No.	Tests	1st month results	2nd month results	3rd month results
1	Appearance	Passes	Passes	Passes
2	Average weight (mg)	1518	1515	1510
3	Hardness (Kg/cm^2)	13	12.8	12.5
4	*In- vitro* drug release	Passes	Passes	Passes
5	Drug content (%) (M. HCl, Miglitol)	99.2, 99.1	98, 98.3	97.1, 97.5