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Original Article

Formulation and Evaluation of Sustained Release Matrix Tablets of Glipizide

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Abstract

The purpose of this study was to develop a new monolithic matrix tablet to completely deliver glipizide in a zero order manner over a sustained period. Two approaches were examined using drug in a formulation that contain polymer like hydroxylpropyl methylcellulose K 100 (HPMCK) and Eudragit L 100. The granules were prepared by wet granulation method and thereby formulated as F-1, F-2. F-3 and F-4 by using the above bring up polymers with other ingredients. The granules of different formulations were evaluated for angle of repose, loose bulk density and tapped density, compressibility index, total porosity, and drug content. The angle of repose and compressibility index (%) ranged from 25.0±0.8 to 28.0±1.1 and 12.92±0.02 to 13.08±0.03, respectively. The results of angle of repose (<30) indicate good flow properties of the granules. This was further supported by lower compressibility index values. The granules showed satisfactory flow properties, compressibility and drug content. All of the formulations showed uniform thickness (C.V< 0.5%), uniform weight with little significance difference were observed with varying formulation composition. In the weight variation test, the pharmacopoeial limit for the percentage of deviation for tablets of more than 130 mg to 324 mg is 7.5 % difference. Technological characterizations (thickness, diameter, weight variation test, drug content, hardness, and friability) were conceded with the formulated matrix tablet and *in vitro* drug release was measured by means of dissolution apparatus. Of the various formulation distinguished, out of which, the formulation (F3) were preferred to be full of 30 mg of HPMCK and 35 mg of Eudragit L100 was subjected to stability were accomplished studies for three months at 4 °C. The room temperature (25 °C) and (45 °C) with relative humidity 75±5% were maintained and its stability with respect to release pattern. The kinetic release treatment showed that the release of drug follows zero order kinetic (r^2= 0. 9959), Koresmeyer equation gave value of r^2= 0.9853 which was close to one indicating that the drug was released by zero order kinetic. According to Koresmeyer equation, the formulation F-1, F-2, and F-4 showed the regression values of 0.9823, 0.9785, and 0.9742, respectively. The identical plot for (log cumulative percentage drug release vs time) for Koresmeyer-Peppas equation indicated a good linearity for the commercially available sustained release tablet and formulation F-3 with regression values of 0.9619 and 0.9959, respectively. Scanning electron microscope confirmed both diffusion and erosion mechanism for the optimized batch of matrix tablet F-3. Results suggest that the formulated tablet F-3 of glipizide could perform therapeutically better than the reachable marketed drug leading to improve better efficacy.

Keywords: Eudragit L 100; Glipizide; HPMC K 100; Matrix tablet; Sustained release.
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1. Introduction

Increased complications and expense involved in marketing of new drug entities has focused greater attention on development of sustained release (SR) or controlled release (CR) drug delivery systems [1].Sustained or controlled release delivery systems can achieve predictable and reproducible release rates, extended duration of activity for short half - life drugs, decreased toxicity, and reduction of required dose, optimized therapy and better patient compliance [2, 3]. Matrix type sustained delivery systems are popular because of their ease of manufactures. It excludes complex production procedure such as coating and pellitization during manufacturing and drug release from the dosage form. It is controlled mainly by the type and proportion of the polymers used in the preparation. Hydrophilic polymer matrix is widely used for formulating a sustained release dosage form [4, 5].

The hydrophilic polymer selected for the present study was hydroxylpropyl methyl-cellulose K 100 (HPMC K 100). Hydrophilic polymer matrix system are widely used for designing oral sustained release delivery systems because of their flexibility to provide a desirable drug release profile, cost effectiveness, and broad regulatory acceptance. HPMC K 100 forms transparent tough and flexible films from aqueous solution. The films dissolve completely in the gastrointestinal tract at any biological pH and provide good bioavailability of the active ingredient. However, the use of hydrophilic matrix alone for extending drug release for highly water soluble drugs is restricted due to rapid diffusion of the dissolved drug through the hydrophilic matrix. For such drugs it becomes essential to include hydrophobic polymers in the matrix system as Eudragit L 100. Among the several polymers available as possible matrix forming materials, methacrylic resins (Eudragit) appear particularly attractive [8], due to their high chemical stability, good compatibility properties and large variety of products with different physicochemical characteristics present on the market.

Glipizide is an oral hypoglycemic agent, which is a commonly prescribed drug for the treatment of patients with type II diabetes [7]. It is used adjunct to diet to the management of type II (non-insulin dependent) diabetes mellitus in patients whose hyperglycemia cannot be controlled by diet and exercise alone. Glipizide stimulates insulin secretion from the β cells of pancreatic islets tissue, increases the concentration of insulin in the pancreatic vein and may increase the number of insulin receptors. Glipizide is a weak acid (pKa = 5.9) practically insoluble in water and acidic environment and highly permeable (class II) drugs according to the Biopharmaceutical Classification System (BCS) [9]. The oral absorption is uniform, rapid and complete with a bioavailability of nearly 100% and an elimination half-life of 2-4 hours [9]. Glipizide is reported to have a short biological half-life (3.4±0.7 h) requiring it to be administered in 2 to 3 doses of 2.5 to 10 mg per day [10]. SR formulations that would maintain plasma levels of drug for 8 to 12 hrs might be sufficient for once a day dosing for glipizide. SR products are needed for glipizide to prolong its duration of action and to improve patient compliance [11].

2. Materials and methods

2.1. Materials

Glipizide, HPMC K-100, Eudragit L-100, were received as gift samples from Aravind Remedies (AR), Chennai. Lactose, povidone, iso propyl alcohol (IPA), aerosil, magnesium stearate, was of AR Grade.

2.2. Methods

2.2.1. Preparation of matrix tablets

Different tablet formulations were prepared by wet granulation technique (Table 1). All the powders were passed through sieve number 80. Required quantities of drug and polymer

Table 1. Composition of sustained release matrix tablets of glipizide.

S. No	Ingredients	Formulation F1	Formulation F2	Formulation F3	Formulation F4
1.	Glipizide (mg)	10	10	10	10
2.	HPMC-K100 (mg)	27.5	25	30	32.5
3.	Lactose (mg	17.5	25	10	15
4.	Eudragit 100 (mg)	30	25	35	27.5
5.	Povidone (mg)	5	5	5	5
6.	Iso propyl alcohol (IPA) (ml)	50	50	50	50
7.	Aerosil (mg)	0.5	0.5	0.5	0.5
8.	Magnesium Stearate (mg)	1	1	1	1

were mixed thoroughly and a sufficient volume of granulating agent was added povidone in isopropyl alcohol, slowly. After enough cohesiveness was obtained the mass was sieved through sieve number 22. The granules were dried at 55±5 °C for one hour. Once dried the granules retained on sieve number 44 were mixed with magnesium stearate and aerosil for 2 min. The practical weight of tablets, were calculated based on the drug content of the granulations and the tablets were compressed using double punch tableting machine, equipped with beveled flat faced punch of size 8 mm of diameter (Cadmach Machinery Company, Ahmedabad, India). Each tablet contained 10 mg of glipizide and other pharmaceutical ingredients as listed in Table 1. Prior to the compression the granules were evaluated for several tests.

2.3. Evaluation of granules

2.3.1. Angle of repose

The angle of repose of granules was determined by the funnel method. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation [11].

$$\text{Tan } \theta = h/r$$

Where 'h' and 'r' are the height and radius of the powder cone, respectively.

2.3.2. Bulk density

Both loose Bulk density (LBD) and tapped density (TBD) were determined. A calculated quantity of 2 g of powder from each formula was introduced into a measuring cylinder and tapped for certain time until no further change in volume was noted. LBD and TBD were calculated using the following formula.

LBD= Weight of the powder/ Volume of the packing

TBD = Weight of the powder/ Tapped Volume of the packing

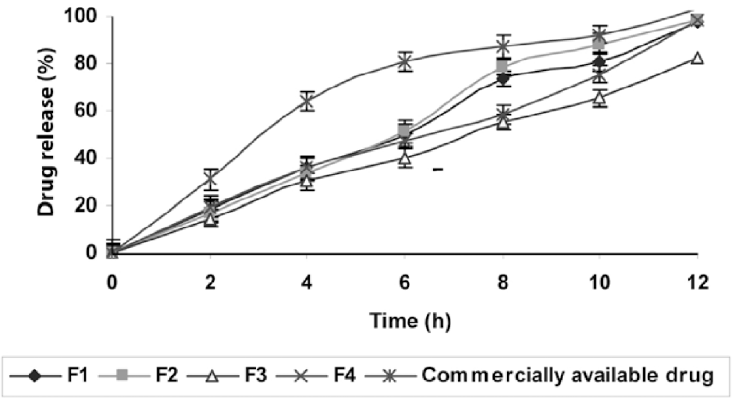

Figure 1. Percentage of drug release from the marketed tablet and formulated tablets (n=4, mean±SE).

2.3.3. Compressibility index

The compressibility Index of the granules was determined by Carr's compressibility index (Equation 1) [12].

Carr's Index (%) = (TBD-LBD) ×100 / TBD (Equation 1)

2.3.4. Total porosity

Total Porosity was determined by measuring the volume occupied by a selected weight of a powder (V bulk) and the true volume of the granules V the space occupied by the powder exclusive of spaces greater than the intermolecular space) (Equation 2) [13].

Porosity (%)=[V bulk-V/ V Bulk]×100 (Equation 2)

2.3.5. Drug content

An accurately weighed amount of powdered glipizide granules (15 mg) equivalent of glipizide was extracted with water and the solution was filtered through 0.45 µ membrane. The absorbance was measured spectrophotometrically at 276 nm after suitable dilution.

2.4. Evaluations of tablets

2.4.1. Thickness

The thickness of the tablets were determined using a Digital Caliper (Mitutoyo, Digimatic Caliper, New Delhi, India) 20 tablets from each batch were used and average values were calculated.

2.4.2. Weight variation test

To study the weight variation, 20 tablets of each formulation were selected at random and determine their average weight [14]. Not more than 2 of the individual weights may deviate from the average weight by more than the % deviation and none should deviate by more than twice that percentage (Limit for not more than 130 to 324 mg is 7.5 %.).

2.4.3. Drug content

Twenty Tablets were weighed individually and the drug was extracted in water. The drug content was determined by filtering the solution through 0.45 µm. The drug content was analyzed after suitable dilution by spectrophotometrically at 276 nm.

2.4.4. Hardness and friability

For each formulation, the hardness and friability of 20 tablets each were determined using the Monsanto Hardness Tester and Roche Friabilator (Cadmach, Ahmedabad, India), respectively.

2.5. In vitro release studies

The *in vitro* dissolution studies were performed using USP -22 type I dissolution (Electro Lab, TDT -08 L, Mumbai, India)

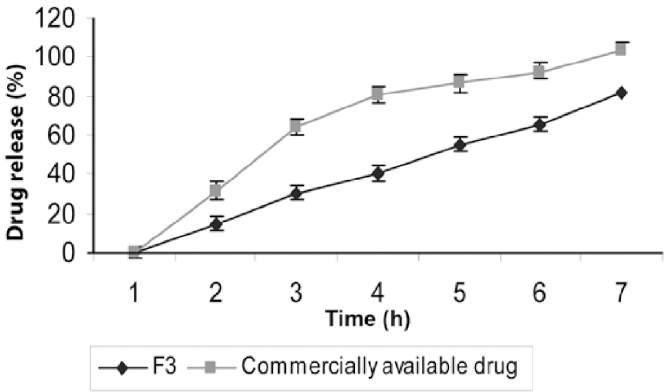

Figure 2. Percentage of drug release from the marketed tablet and formulated tablet, (n=4, mean±SE).

apparatus 37±5°C, at 50 rpm. Using 900 ml of 0.1 N HCl for first 2 hr and phosphate buffer of pH 6.8 from 2-12 hr. An aliquot (5 ml) of the sample solution was withdrawn at predetermined time intervals , filtered through a 0.45 μm membrane filter, diluted suitably and analyzed spectrophotometrically at 276 nm (Shimadzu Model 1601). An equal amount of fresh dissolution medium was replaced immediately after withdrawal of the test sample. The release studies were conducted in triplicate.

2.6. Optimum release profile

Optimum release profile for once daily SR formulation was calculated by the Equation 3 using available pharmacokinetic data [15].

$$Dt = Dose\ (1+ 0.693 \times t / t\ ½) \quad \text{(Equation 3)}$$

Where Dt is total dose of drug, dose is dose of the immediate release part, t is time during which the sustained release is desired (24 h) and t ½ is half -life of the drug (3 h).

The optimum formulation was selected on the above equation so that it could attain complete and controlled drug release upon "trading off" various response variables; the following maximizing criteria were adopted.

2.7. Kinetic release profile

To study the release kinetics, data obtained from *in vitro* drug release studies were plotted in various kinetic models, zero order (Equation 4) as cumulative amount of drug released vs time, first order (Equation 5) as log cumulative percentage of drug remaining *vs.* time, and Higuchi's model (Equation 6) as cumulative percentage of drug released *vs.* square root o f time.

$$Q=Ko.t \quad \text{(Equation 4)}$$

Where 'Ko' is the zero -order rate constant expressed in units of concentration / time and t is the time in hours. A graph of concentration vs. time would yield a straight line with a slope equal to Ko and intercept the origin of the axes [16].

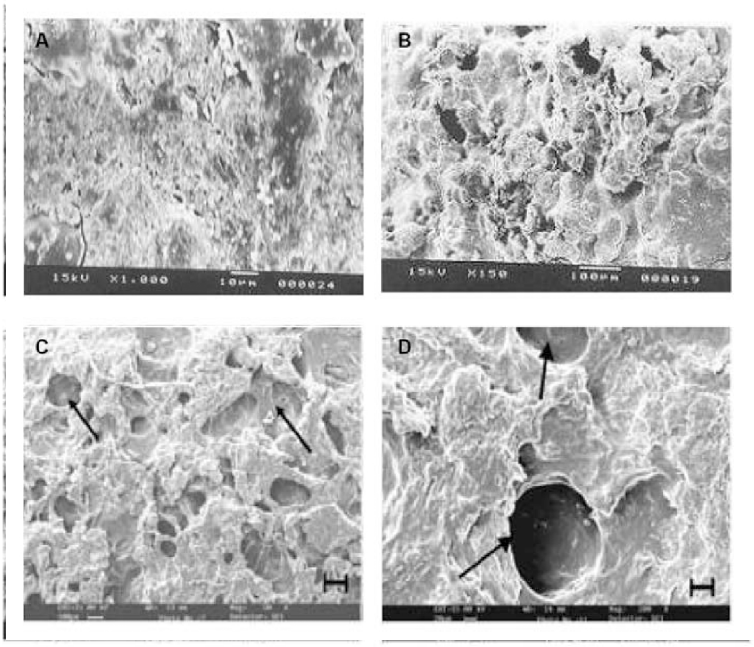

Figure 3. Scanning electron photographs of the matrix tablet formulation F3 taken at different time intervals after the dissolution experiment. A, B, C and D revealing the dissolution studies at the time of 0, 2, 8, 12 h, respectively.

Table 2. Characterisation of granules and formulated glipizide tablets.

Formulation	Angle of repose (°)	Bulk density (g/ml)	Tap Density (g/ml)	Carr's index (%)	Total drug content (%)	Drug content (%)	Friability (%)	Hardness (Kg/cm^2)	Weight variation(%)
F1	28±1.1	0.43	0.53	13.08±0.02	98±3.6	98.3±4.3	±0.31	6.3±0.2	0.250
F2	25±0.8	0.37	0.52	12.95±0.03	99±3.9	99.2±4.0	±0.31	6.1±0.2	0.250
F3	27±0.9	0.36	0.50	12.92±0.02	99.5±3.7	99.5±3.0	±0.32	6.0±0.1	0.250
F4	26±0.6	0.39	0.53	12.95±0.03	99±4.1	98.7±4.0	±0.29	6.2±0.1	0.250

All values are expressed as mean±S.D. (n=3).

$$\text{Log } C = \text{Log } Co - kt/2.303 \quad \text{(Equation 5)}$$

Where 'Co' is the initial concentration of drug, 'k' is the first order constant, and t is the time [17].

$$Q = k\sqrt{t} \quad \text{(Equation 6)}$$

Where 'K' is the constant, reflecting the design variables of the system and t is the time in hours. These models fail to explain drug release mechanisms due to the swelling (upon hydration) along with gradual erosion of the matrix. Therefore the dissolution data was also fitted to the well known Koresmeyer equation (Equation 7) which is often used to describe the drug release behavior from polymer systems.

$$\text{Log } (Mt/M\alpha) = \log K + n \text{ Log} t \quad \text{(Equation 7)}$$

Where 'Mt' is the amount of the drug release at time 't', 'Mα' is the amount of drug release after infinite time and 'K' is a release rate constant incorporating structural and geometric characteristic of the tablet and 'n' is the diffusion exponent indications of the mechanism of drug release. To clarify the release exponent for different batches of matrix tablet the log value of percentage of drug dissolved was plotted against log time for each batch according to the equation. A value of n=0.45 indicates Fickian (case -I) release: >0.45 but <0.89 for non-Fickian (Anomalous) release and >0.89 indicates super case II type of release. Case II generally refers to the erosion of the polymeric chain and anomalous transport (non-Fickian) refers to a combination of both erosion and diffusion controlled drug release [17].

2.8. Accelerated stability studies

Tablets from optimized formulated batch F3 was packed in an air tight high density polythene bottles and kept at 45 °C with 75±5% RH for 3 months as per International Congress on Harmonization states (ICH) guidelines. Samples were withdrawn at 0, 30, 60 and 90 days of storage and evaluated for appearance, hardness and drug content.

2.9. Scanning electron microscopy

The optimized tablet samples were removed from the dissolution apparatus at predetermined time intervals and sectioned through an undisturbed portion of the sample holder so as to present a cross section of the tablet to the microscope. Samples were coated with gold and visualized under scanning electron microscope (SEM).

3. Results and discussion

3.1. Evaluation of granules

Granulation is the key process in the production of tablet dosage form involving the sustained release of a drug from coated to matrix type particles. A granule is the aggregation of constituent particles that is held together by the presence of bonds of restricted strength. Physical properties of granules such as specific surface area, shape, hardness, surface characteristics, and size can significantly affect the rate of dissolution of drugs contained in the heterogeneous formulation. The granules of different formulations were evaluated for angle of repose, LBD, TBD, compressibility index, total porosity, and drug content (Table 2). The angle of repose and compressibility index (%) ranged from 25.0±0.8 to 28.0±1.1 and 12.92±0.02 to 13.08±0.03, respectively. The

Table 3. Correlation coefficients according to different kinetic equations used for describing glipizide release behavior.

Formulation	Zero Order	First Order	Higuchi model	Korsmeyer model	
		r^2		n	r^2
F1	0.9932	-0.8923	0.9727	0.6759	0.9823
F2	0.9879	-0.9124	0.9707	0.7280	0.9785
F3	0.9959	-0.9505	0.9695	0.6747	0.9853
F4	0.9867	-0.8123	0.9510	0.6184	0.9742
Commercially available tablet	0.9619	-0.6109	0.9922	0.4807	0.9957

results of angle of repose (< 30) indicate good flow properties of the granules [18]. This was further supported by lower compressibility index values (Table 2). Generally, compressibility index values up to 15% result in excellent flow properties. The results of LBD and TBD ranged from 0.36 to 0.43 and 0.50 to 0.53, respectively. The percentage porosity values of the granules ranged from 26.92 to 37.61%, indicating that the packing of the granules may range from close to loose packing and also further confirming that the particles are not of greatly different sizes. Generally, a percentage porosity value below 26% shows that the particles in the powders are of greatly different sizes and a value greater than 48% shows that particles in the powder are in the form of aggregates or flocculates [19]. The drug content in the weighed amount of granules of all formulations was found to be uniform.

3.2. Technological characteristics of glipizide matrix tablet and drug content

The tablets of different formulations were subjected to various evaluation tests, such as thickness, diameter, and uniformity of drug content, hardness, and friability. The results of these parameters are given in Table 2. All the formulations showed uniform thickness (C.V.<0.5%), uniform weight with little significance difference (p>0.1) were observed with varying formulation composition. In the weight variation test, the pharmacopoeial limit for the percentage deviation for tablets of more than 130 mg to 324 mg is 7.5% difference. The average percentage deviation of all tablet formulations was found to be within the said limit, and hence all formulations passed the test for uniformity of weight as per official requirements [20]. Drug content was found to be uniform among different batches of the tablets (n=20) and ranged from 98.3±0.4 to 99.5±0.3. The hardness of the tablets (n=10) ranged from 6.0±0.1 to 6.3±0.2 kg / cm^2. The percentage friability of the tablets (n=10) ranged from 0.079±0.310 to 0.088±0.12 %. The percentage friability for all the formulations were below 1% indicating that the friability is within the prescribed limits [22]. All the tablet formulations showed acceptable pharmacopoeial properties and complied with the in house specifications for weight variation, drug content, hardness, and friability.

3.3. Dissolution studies

Ideally, an extended release tablet should release the required quantity of drug with predetermined kinetics in order to maintain an effective drug plasma concentration. To achieve this, the tablet should be formulated so that it releases the drug in a predetermined and reproducible manner. By considering the drugs biopharmaceutic and pharmacokinetic profile, one can determine the required release from the tablet [23]. Figures 1 and 2 shows the *in vitro* drug release profile of glipizide SR matrix tablets. Visual observation of the tablets during dissolution testing revealed that swelling was dominant during the test procedure. According to the theoretical release pattern, once daily glipizide SR formulation

Table 4. Physical and chemical parameters of formulated glipizide tablets during stability studies at 45 °C.

Formulation	Time	Appearance	Hardness	Drug content
F3	Initial	Pale White	6.0±0.21	99.52±0.70
	After 30 days	Pale White	5.6±0.20	99.53±0.65
	After 60 days	Pale White	6.1±0.21	99.52±0.55
	After 90 days	Pale White	5.6±0.2 0	99.52±0.68

should release 0.303 mg in 1 h and 7.28 mg per hour up to 24 h.

The release rate of tablets prepared with higher quantity of Eudragit L 100 reduces the permeation of water inside the granules [24]. However, the drug release in the formulation F1, F2, and F4 were initially in more amounts and released in faster rate within 12 h. This may be due to the amount of HPMC K 100 and Eudragit L 100 present in the formulations. The initial release is about 14-20% of the drug during the 2nd h. This phenomenon may be attributed to surface erosion or initial disaggregation of the matrix tablet prior to gel layer formation around the tablet core. Tablets containing release modifiers (formulation F3) exhibited slow release of glipizide as compared to commercially available SR tablet (Glytop*) (Figure 2). Formulation F 3 showed 55% of the drug release in 8 hr where as commercially available SR tablet showed the release of 87% in 8 h (Figure 1). Formulation F1, F2, and F4, showed 74 %, 78 %, and 59 %, of the drug release respectively in 8 hr. When compared with other formulations like F1, F2 and F4, formulation F3 contains more amount of Eudragit L 100. However, when HPMC K 100 was combined with Eudragit L 100 no burst release (less than 20%) was observed in formulations, when compared to the commercially available SR tablet, which has highly significant release.

3.4. Kinetic release data

The kinetic release data for all the models is shown in Table 3. Drug release data of all the formulation fit good to the zero order kinetic describes that the systems is independent of concentration. Drug release of the formulation F1, F2 and F4 had the regression data of 0.9932, 0.9879, and 0.9867, respectively, follows zero order kinetics. According to Koresmeyer equation, the formulation F1, F2, and F4 showed the regression values of 0.9823, 0.9785, and 0.9742, respectively. The corresponding plot for (log cumulative percentage drug release vs time) for Koresmeyer-Peppas equation indicated a good linearity for the commercially available SR tablet and formulation F3 with regression values of 0.9619 and 0.9959, respectively. The release component *n* was 0.6747 and 0.4807 respectively which appears to indicate a coupling of the diffusion and erosion mechanism so called anomalous diffusion may indicate that the drug release is controlled by more than one process. Release of the drug from a matrix tablet containing hydrophilic polymers generally involves factors of diffusion. Diffusion is related to transport of drug from the dosage matrix into the *in vitro* study fluid depending on the concentration. The Eudragit present helped in retaining the drug in the matrix and did not allow rapid diffusion of the drug from the matrix. Reddy *et al*. were reported the similar results with a matrix tablet (n value of 0.71) [25]. Fassihi and Ritschel description by means of a matrix tablet (n value of 0.7) [26]. Basak et al. with a matrix tablet of ambroxol hydrochloride with an *n* value of 0.542 [27]. The present learning indicate that the release mode of formulations assortment as of 0.6184 to 0.7280. The stability studies revealed that there was no significant change in hardness, friability, drug content and dissolution profiles of the formulation F3. Thus, formulation was

constant at different circumstances of temperature.

3.5. Scanning electron microscopy

Scanning electron microscopy (SEM) study confirmed both diffusion and erosion mechanism from the optimized batch of matrix tablet (formulation F3). The results were summarized in Figure 3. The photograph of the matrix tablet taken at different time intervals after the dissolution experiment demonstrated. If reflects the matrix was intact and pores had formed through out the matrix. On the other hand, SEM photomicrographs also be a sign of the surface of the fresh tablet did not illustrate any pores. These photomicrographs taken at the intervals also revealed formation of gelling structure and indicating the possibility of swelling of matrix tablets. Thus, the formation of both pores and gelling structure on the tablet indicates the involvement of both erosion and diffusion mechanism to be respectively formed sustaining the release of glipizide from matrix tablets.

4. Conclusion

The mixture of (HPMC K100 and Eudragit L100) matrix demonstrates to particularly suitable obtaining directly compressed with appropriate technological properties and well reproducible release profiles.

Simplicity of the formulation, ease of manufacturing and complete dissolution of system is among the advantages of the developed matrix formulations. The results of release studies indicated the possibility of achieving a suitable modulation of matrix release rate by opportunely varying ratio of matrix tablets, taking advantage at the same time of moderate swelling properties of Eduragit. The kinetics of drug release was shown to be in accordance with kinetics of hydration/ swelling and Erosion of HPMC K 100 and Eudragit L100. Significantly greater swelling/hydration observed in HPMC K 100 is attributed due to higher concentration of the polymer and inherent water retention characteristic of HPMC. The stronger gel structure of HPMC K based formulation relative to that of Eudragit may provide superior quality *in vivo* performance in terms of matrix resistance to destructive forces within GIT. Therefore, further studies will be performed for the final setting up of the proposed dosage form, aimed on one hand at developing a gastro-resistant coating able to effectively protect the drug from acid degradation, and on the other, at adequately improving drug release rate, by adding suitable canalizing agents to the polymeric matrix.

References

[1] Gwen MJ, Joseph RR. In: Banker GS and Rhodes, CT, (editors). *Modern pharmaceutics*. 3rd ed. Vol 72. New York: Marcel Dekker Inc., 1996; p. 575.

[2] Chein YW. *Novel drug delivery systems*. 2nd ed. New York: Marcel Dekker Inc., 1997; pp.1-42.

[3] Ritchel WA. Biopharmaceutic and pharmacokinetic apects in the design of controlled release per-oral drug deliver system. *Drug Dev Ind Pharm* 1989; 15: 1073-103.

[4] Reddy KR, Mutalik S, Reddy S. Once daily sustained release matrix tablets of nicorandinal formulation *in vitro* evaluation. *AAPS Pharm Sci Tech* 2003; 4: 1-9.

[5] Mohammed AD, James LF, Michael HR, John EH, Rajabi-Siahboomi AR. Release of propranolol hydrochloride from matrix tablets containing sodium carboxymethylcellulose and hydroxypropylmethylcellulose. *Pharm Dev Tech* 1999; 4: 313-24.

[6] Verma RK, Garg S. Development and evaluation of osmotically controlled oral drug delivery system of glipizide. *Eur J Pharm Biopharm* 2004; 57: 513-25.

[7] Jamzad S, Fassihi R. Development of controlled release low dose class II drug-glipizide. *Int J Pharm* 2006; 312: 24-32.

[8] Rodriguez L, Caputo O, Cini M, Cavallari C, Grecchi R. *In vitro* release of theophylline from directly-compressed matrices containing methacrylic acid copolymers and/or dicalcium phosphate dihydrate. *Ill Farmaco* 1993; 48: 1597-604.

[9] Sweetman SC. *Martindale*, *the complete drug reference*. 34th ed. London: Pharmaceutical Press,

2005; pp. 324-48.
[10] Patel JK, Patel RP, Amin AF, Patel MM. Formulation and evaluation of glipizide microspheres. *AAPS Pharm Sci Tech* 2005; 6: 49-55.
[11] Chowdary KPR, Rao YS. Design and *in vitro* and *in vivo* evaluation of mucoadesive microcapsules of glipizide for oral controlled release. *AAPS Pharm Sci Tech* 2003; 4: 1-6.
[12] Cooper J, Gunn C. Powder flow and compaction. In: Carter SJ, (editor). *Tutorial pharmacy*. New Delhi: CBS Publishers and distributors, 1986; pp. 211-33.
[13] Lachman L, Lieberman HA, Kanig JL. *The theory and practice of industrial pharmacy*. Philadelphia: Lea & Febieger, 1970; pp. 68-9.
[14] *The Pharmacopoeia of India*. New Delhi: Controller of Publication, 1996; pp.736.
[15] Rawlins EA. *Bentley's text book of pharmaceutics*. London: Cassell and Colloer Macmillian, 1977.
[16] Hadjioannou TP, Christain GD, Koupparis MA. *Quantitative calculations in pharmaceutical practice and research*. New York: VCH Publishers Inc., 1993; pp. 345-8.
[17] Bourne DW. Pharmacokinetics. In: Banker GS, Rhoides CT, (editors). *Modern pharmaceutics*. 4th ed. New York: Marcel Dekker Inc. 2002; 67-92.
[18] Aulton ME, Wells TL. *Pharmaceutics, the science of dosage form design*. London: Churchill, Livingstone, 1988.
[19] Martin A. *Physical pharmacy*. Baltimore: Lippincott Williams and Wilkins, 2001; p. 423.
[20] Lachman L, Lieberman HA, Kanig JL. *The theory & practice of industrial pharmacy*. Mumbai: Varghese Publishing House, 1987; p. 293.
[21] Sanchez-Lafuente C, Faucci MT, Fernandez-Arevels M, Alvarez FJ, Rabasco AM, Mura P. Development of sustained release matrix tablets of didanosine contain is methacyclic and ethyl cellulose polymers. *Int J Pharm* 2002; 234: 213-21.
[22] Saravanan M, Natraj KS, Ganesh KS. Hydroxypropyl methyl cellulose based cephalexin extended release tablets: Influence of tablet formulation, hardness and storage on *in vivo* release kinetics. *Chem Pharm Bull* 2003; 51: 978-83.
[23] Defang O, Shufang NL. *In vitro* and *in vivo* evaluation of two extended release preparations of combination metformin and glipizide. *Drug Dev Ind Pharm* 2005; 31: 677-85.
[24] Saravanan M, Natraj KS, Ganesh KS. The effect of tablet formulation and hardness on *in vitro* release of cephalexin from Eudragit L100 based extended release tablets. *Biol Pharm Bull* 2002; 25: 4541-5.
[25] Reddy KR, Mutalik S, Reddy S. Once daily sustained release matrix tablets of nicorandrail, formulation and *in vitro* evaluation. *AAPS Pharm Sci Tech* 2003; 4: 61.
[26] Fassihi RA, Ritschel WA. Multiple layer, direct compression controlled release system, *in vitro* and *in vivo* evaluation. *J Pharm Sci* 1993; 82: 750-4.
[27] Basak SC, Jayakumar Reddy BM, Lucas Mani KP. Formulation and release behavior of sustained release Ambroxol hydrochloride HPMC matrix tablet. *Indian Pharm Sci* 2006; 5: 594-7.