

PREPARATION AND IN VITRO DISSOLUTION OF GLIPIZIDE SUSTAINED RELEASE TABLETS

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Abstract

Glipizide is an oral blood glucose lowering agent having short biological half life (2-4 hrs). Since oral sustained release dosage form of this drug is less frequently available worldwide, therefore the present study was conducted to develop formulation of glipizide using ethyl cellulose (hydrophobic), high viscosity grades of hydroxypropyl methylcellulose (hydrophilic) and Kollicoat SR (hydrophobic-hydrophilic mixed). All the polymers were incorporated separately in the matrix system using wet granulation technique. In vitro dissolution studies were conducted in 450 ml 0.1M NaOH solution for 12 hrs testing intervals. Dissolution data indicated that as the amount of various polymers increased, the release rate of glipizide form matrix tablet was decreased. However, more sustaining effect was produced by HPMC based matrix tablets compared to EC or Kollicoat SR-based matrix tablets. However, HPMC-based formulation comprising 10% glipizide, 50% HPMC, 39% lactose, and 1.0% magnesium stearate produced more linear release profile and comparable to reference product, Glipizide XL.

Key Words: *Glipizide, HPMC, Polyvinyl acetate, Kollicoat SR, Sustained release*

Glipizid Uzatılmış Salım Gösteren Tabletlerinin Hazırlanması ve In Vitro Çözünme Hızı

Glipizid biyolojik yarılanma ömrü kısa (2-4 saat), oral kullanılan bir kan glukozu düşürücü bir maddedir. Bu ilacın uzatılmış salım gösteren şeklinin dünyada daha az bulunması nedeniyle, bu çalışma etilselüloz (hidrofobik), yüksek viskoziteli hidroksipropil metilselüloz (hidrofilik) ve Kollicoat SR (hidrofobik-hidrofilik karışımı) kullanılarak glipizid formülasyonu geliştirmek üzere gerçekleştirildi. Tüm polimerler yaş granülasyon tekniği kullanılarak matriks system içine ayrı ayrı eklendi. In vitro çözünme hızı çalışmaları, 450 mL 0.1 M NaOH çözeltisinde 12 saat süreyle yürütüldü. Çözünme hızı bulgularına göre, farklı polimerlerin miktarları arttıkça glipizidin matriks tabletten salımı azaldı. Bununla birlikte, EC veya kollicoat SR matriks tabletler ile karşılaştırıldığında, HPMC esaslı matriks tabletlerle daha fazla uzatılmış etki elde edildi. Diğer yandan, HPMC esaslı ve %10 glipizid, %50 HPMC, %39 laktöz ve %1 magnezyum stearat içeren formülasyon, referans ürün Glipizide XL'e göre daha doğrusal bir salım profili gösterdi.

Anahtar Kelimeler: *Glipizid, HPMC, Polivinil asetae, Kollicoat SR, Uzatılmış salım*

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INTRODUCTION

Glipizide is an oral blood glucose lowering weak acidic drug ($pK_a = 5.9$), practically insoluble in water and acidic environment (1,2). It has 100% bioavailability in the body with shorter half life (2-4hrs) and considered to be good candidate for reducing dose frequency as well as more compliance in diabetics.

Matrix system for oral drug administration has been prepared by direct compression and wet granulation as reported and documented in various studies (3-6). Drug release from sustained release matrix tablets can be strongly influenced by the proportion of matrix forming polymer and the dimensions and geometry of the tablets (7). The least complicated approaches to manufacture sustained release matrix tablets consists of a drug dispersed with retardant materials and additives to form tablets by wet granulation or direct compression (8-11). Several workers reported that the rate of drug release from matrix is affected by the composition of the matrix, shape, pH of dissolution fluid, drug solubility, external agitation, amount of drug and the porosity of the matrix (12-14). Depending upon the chemical nature, various polymers such as ethyl cellulose (hydrophobic), hydroxypropylmethylcellulose (hydrophilic) and polyvinyl acetate/Kollicoat SR (hydrophobic-hydrophilic mixed) were selected in the present study for achieving the sustained release effects of these polymers. Kollicoat SR is a physical mixture of 80% hydrophobic polyvinyl acetate, 19% hydrophilic povidone (150). ethyl cellulose (EC) is cellulose ether and has good stability at varying pH values. On the other hand hydroxypropyl methylcellulose (HPMC) is a methylcellulose modified with a small amount of propylene glycol with pH independent solubility and has been found to be very versatile material for the formulation of soluble matrix (15-17).

EXPERIMENTAL

Materials

Glipizide (Pharmedic Laboratories, Lahore, Pakistan), Hydroxypropylmethylcellulose 15,000cps (Colorcon, India), Ethyl cellulose 45cps (Highnoon laboratories, Pakistan), Kollidon SR (BASF, Germany), Lactose (BDH, Poole, England), Isopropyl alcohol (Merck, Germany), Magnesium stearate (Fluka, Buchs, Germany), Sodium hydroxide (Merck, Germany) were used as received.

Matrix Tablets

Sustained release glipizide tablets were prepared by employing EC (10%-25%w/w), HPMC (20%-60% w/w) and Kollidon SR (20-60% w/w) using wet granulation method. For these matrix systems (Table 1), glipizide, lactose and polymer were weighed individually and sieved through mesh size No. 20 and were blended in a Kenwood mixer for 5 minutes and granulated with small amount of isopropyl alcohol and then wet mass was sieved through mesh No. 8 and dried at 60°C for 1 hour in an air circulated oven (Mettert, Germany). The dried granules were passed through mesh No. 10 and the fractions of granules retained on the sieve were discarded. In the end magnesium stearates (1% w/w) was used for lubrication of all types of granules and were stored in air tight polyethylene bags. The weight of granules was adjusted to 200 mg and compressed separately using single punch machine (Emmy, Pakistan).

Table 1. Formulations of Glipizide matrix tablets (EC, ethyl cellulose, HPMC, hydroxypropylmethyl cellulose and Kollicoat SR, polyvinyl acetate/povidone).

Ingredients %	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14
Glipizide	10	10	10	10	10	10	10	10	10	10	10	10	10	10
EC	10	15	20	25	-	-	-	-	-	-	-	-	-	-
HPMC	-	-	-	-	20	30	40	50	60	-	-	-	-	-
Kollicoat SR	-	-	-	-	-	-	-	-	-	20	30	40	50	60
Lactose	79	74	69	64	69	59	49	39	29	69	59	49	39	29
Magnesium Stearate	1	1	1	1	1	1	1	1	1	1	1	1	1	1

In Vitro Release Studies

The in vitro drug release profiles of various glipizide matrix tablets were evaluated using USP apparatus II (Pharma Test, Germany). Dissolution test of each preparation was conducted in 450 ml of 0.1M sodium hydroxide solution maintained at $37 \pm 0.5^\circ\text{C}$ and stirred at 50rpm. At pre-determined time intervals (0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 hours) an aliquot amount (5ml) of dissolution media was drawn by an automatic sampler unit (Watson Marlo, Stockholm, Sweden). Samples were filtered through 10 μm Sinter filter (Pharma Test, Hainburg, Germany) to remove suspended and insoluble tablet components and analyzed by UV spectrophotometer (Shimadzu, Kyoto, Japan) at 276nm. In the data analysis of each formulation, cumulative percentage of drug release was calculated using a mean of three samples readings.

RESULTS AND DISCUSSION

The objectives of sustained release delivery systems is to provide desirable in vitro release profiles so that predictable plasma drug levels could be achieved. Formulation factors such as chemical nature and amount of polymer are important considerations when designing a new formulation. Some aspects of a new sustained release matrix tablets for glipizide are presented.

Glipizide release from EC-based tablets

Figure 1 shows the release of glipizide from matrix tablets containing 10-25% of EC. Apparently the release profile is not linear over the entire length of time period. The tablets containing 10% EC, 15% EC, 20% EC and 25% EC, released about 100%, 96 %, 78 % and 71 % respectively in 12 hour testing intervals. As the amount of EC increased, a significant decrease in the rate and extent of drug release was observed. The decrease in drug release rate from EC-based matrix tablets is probably due to formation of ethyl cellulose layers around the individual drug particles. The results found in this study were in good agreement with the reported study (6) in which increasing percentages of EC produced slower drug release rate.

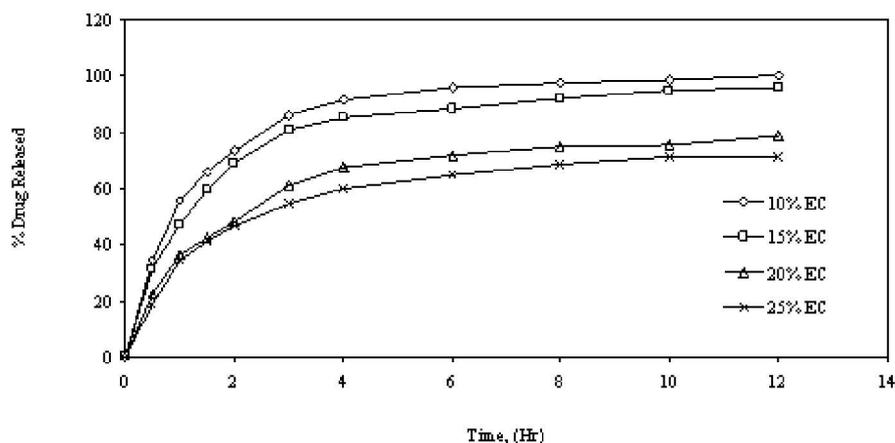


Figure 1. In vitro release profile of glipizide from ethyl cellulose (EC) matrix tablets.

Glipizide release from HPMC-based tablets

The formulation composition for various HPMC-based matrixes is shown in Table 1 while in vitro drug release profiles are presented in Figure 2. It is evident that increasing the percentage of HPMC from 20-60%, the release of glipizide from matrix tablets was reduced in each testing interval. HPMC at higher percentages provided more linear release with a maximum of 74% of drug released in 12 hours. In order to increase both rate and extent of drug release one has to decrease the percentage of polymer. At lesser amount of HPMC in matrix formulations, higher release rates with poor linearity were observed. The observed tailing of release profiles is probably the result of swelling, lack of matrix erosion and greater diffusional pathlength at higher concentrations. Low swelling characteristic of matrix tablets are resulted by increasing the concentration of HPMC as swelling of polymer is dependent upon polymer concentration which in turn lowered the drug release rate. The rate of matrix hydration can also be controlled by changing the concentration of higher molecular weight HPMC. Moreover, higher viscosity grades of HPMC forms higher strength gel, whereas lower viscosity grades possesses lower gel strength (7).

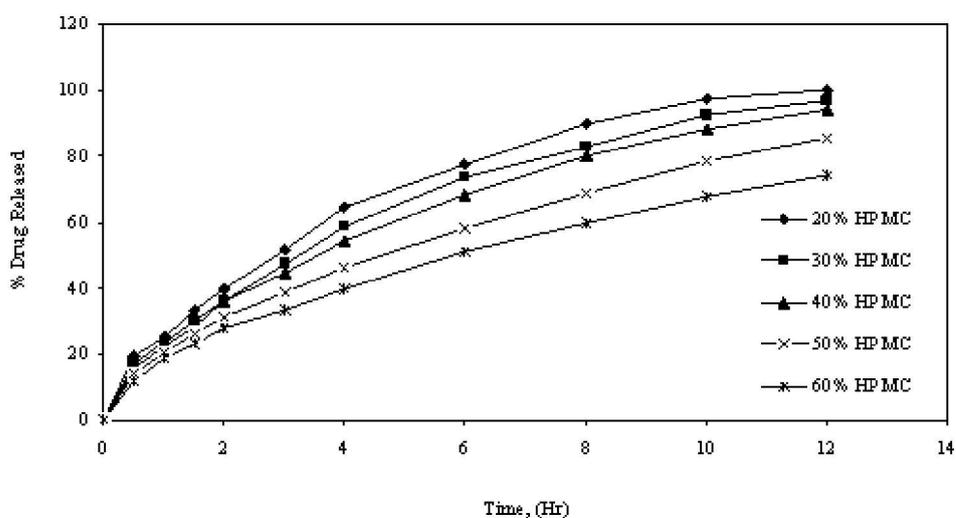


Figure 2. In vitro release profile of glipizide from hydroxypropyl methylcellulose (HPMC) matrix tablets.

Glipizide release from Kollicoat SR-based tablets

Figure 3 shows glipizide release profiles from matrix tablets containing Kollicoat SR (20-60%). It is apparent that the extent of drug release from matrix tablets was appreciably decreased as the amount of polymer increased. By examining the initial part of dissolution profiles, it is clear that the release of glipizide from these matrix tablets was at faster rate during 2 hour testing interval. About 40% of drug was released during this interval from various formulations indicating that Kollicoat SR even in 60% was unable to slow down the release of glipizide at a desirable rate.

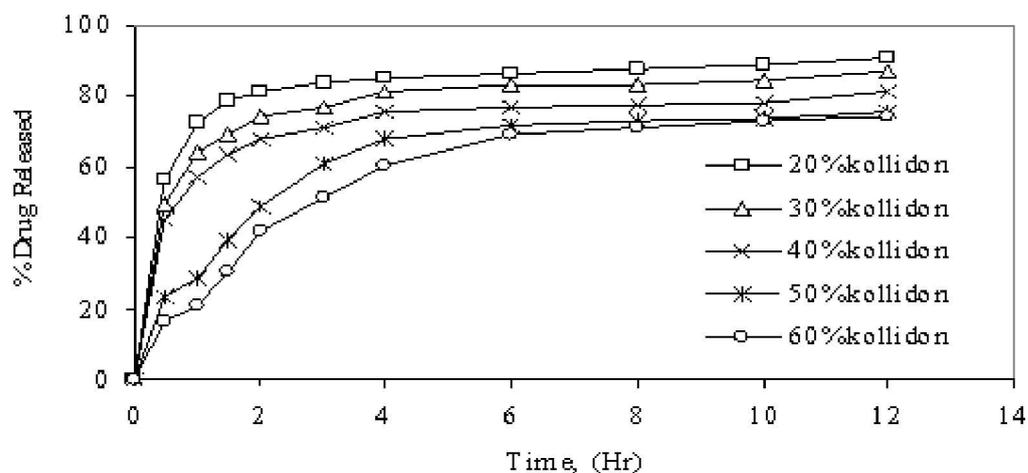


Figure 3. In vitro release profile of glipizide from Kollicoat SR matrix tablets.

However, after 2 hours the extent of drug release was significantly reduced. In vitro release profiles of three different release retardants used in the above studies were also compared in Figure 4. The drug release profiles of 20% each of Kollicoat SR-based, EC-based and HPMC-based matrices are shown indicating that both EC and HPMC had relatively more sustaining effect compared to Kollicoat SR. As hydrophilic povidone is mixed with polyvinyl acetate in Kollicoat SR, therefore povidone might have created greater number of pores on the surface of matrix tablets resulting comparatively faster drug release rate. By examining the initial part (4 hours) of dissolution profiles, both EC and HPMC based tablets were significantly different from Kollicoat SR-based. Therefore, it can be concluded that high viscosity grade HPMC-based formulations could preferably be used in sustaining the release of glipizide.

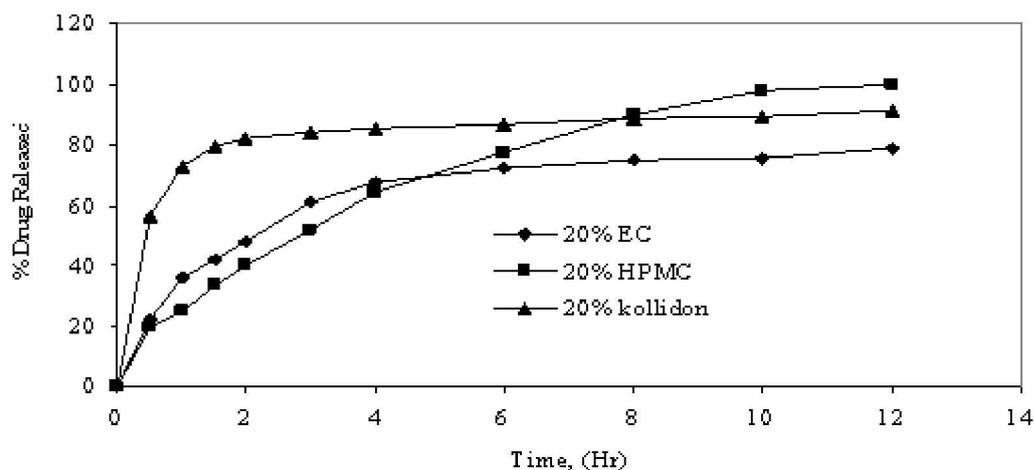


Figure 4. Comparative in vitro release profiles of glipizide from matrix tablets containing 20% each of EC, HPMC and Kollidon.

Comparison of in vitro release profile of Glipizide from HPMC-based (Test) and Glipizide XL tablets (Reference)

Glipizide release profile of HPMC-based formulation (F8, Table 1) was compared with reference, Glipizide XL tablets and is shown in Figure 5. No lag time was observed in either reference or test formulation. The dissolution data shows that during the first six hour period, release rate of test matrix was greater and more linear compared to the reference tablets. Glipizide XL showed slower release rate in the initial 6 hours while faster release rate in the latter part of dissolution testing. However, at the end of 12 hour the percentage release of test matrix tablets was 85.81% compared to 90.86% of the reference tablets. The release data of the two formulations was also fitted in FDA approved f2 test and found to be comparable as the value obtained was greater than 50.

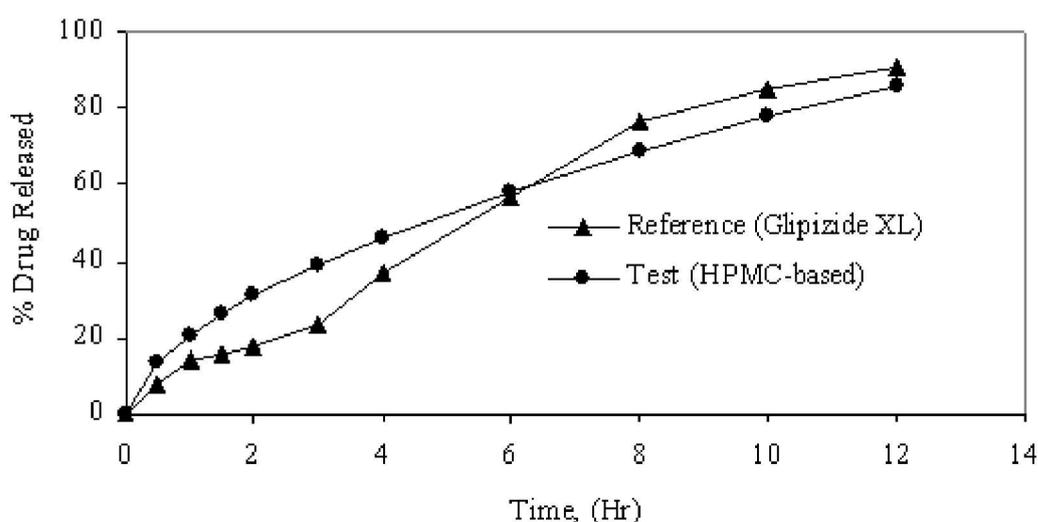


Figure 5. Comparison of in vitro release profiles of glipizide from sustained release reference and test tablets.

CONCLUSION

Sustained release tablets of glipizide were prepared by wet granulation method using Kollicoat SR, EC and HPMC. Increasing the amount of HPMC resulted in decreasing the release rate of drug considerably while Kollicoat SR and EC had less sustaining effect on the release of glipizide. However, the rate of drug release could be readily manipulated in case of HPMC compared to EC or Kollicoat SR by varying the concentrations. Moreover, matrix system comprising 10% glipizide, 50% HPMC, 39% lactose, and 1.0% magnesium stearate produced comparatively more linear release profiles.

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