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In Vitro Comparison of Sustained Release Hydroxypropylmethyl Cellulose and Lipid-Based Matrix Systems of Diltiazem HCl

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Abstract.- A polyglycolised glyceride lipid carrier, Gelucire 50/13 (G50/13) was used to develop sustained release capsules while high viscosity grade HPMC was used to form sustained release tablets of diltiazem HCl. Both HPMC and G50/13 based formulations prepared with increasing polymer to drug ratios showed a substantial decrease in drug release rate. However, G50/13 based matrix containing stearyl alcohol caused greater retardation in release rate compared to G50/13 and provided more linear release profile which was chosen for comparison with HPMC based tablets. The drug release from chosen formula of gelucire was stable at ambient temperature (25 ºC) after aging for six months and essentially independent of pH. Moreover, drug release rate of both sustained release tablets and capsules were found to be comparable with reference product, Herbesser SR.

Keywords: Lipid matrix, Gelucire, diltiazem HCl, sustained release

INTRODUCTION

Lipid based matrix formulations offer many advantages over conventional powder filled/ compressed system that include excellent fill weight, content uniformity, the diminished of dust or cross contamination, easier formulation of oily drugs and improved drug stability. Gelucires are lipids in nature that are essentially identified by their melting point (ranging from 33 to 65ºC) and hydrophilic-lipophilic balance (HLB) (ranging from 1 to 14). In general, gelucire with low HLB are used as coating and matrix agents for sustained release formulations whilst those with high HLB are suitable as bioavailability enhancers (Vila-Jato *et al.,* 1990). Gelucire50/13 was chosen as lipid drug carrier due to its low melting point and its favorable dispersibility in water. Whilst, high viscosity grade hydroxypropylmethyl cellulose (HPMC) was selected among the various swellable hydrophilic polymers for solid matrix tablets due to its rapid hydration, good compression and sustaining drug release characteristics (Huang *et al*., 2003; Gustafsson *et al*., 1999; Fu *et al*., 2004). A hydrated viscous layer or gel layer is usually formed at the tablet periphery, which controls the drug release from the hydrophilic matrix tablets (Kavanagh and Corrigan, 2004).

Diltiazem is an orally and intravenously active therapeutic agent used in the treatment of chronic stable angina and angina due to coronary artery spasm. In healthy individuals, plasma half-life of diltiazem is approximately 3 to 5 hours and must be dosed three to four times daily to maintain the control of heart rate and vasodilatation (Hern'andez *et al*., 1996). The current study was aimed at developing sustained-release formulation of diltiazem HCl using gelucire alone or in combination with stearyl alcohol for lipid matrix capsules and high viscosity grade HPMC for matrix tablet. Moreover, the influence of aging on the release of diltiazem HCl from lipid matrices system has been evaluated. In addition, the optimum solid and lipid matrix formulation was compared with a commercially available sustained release product, Herbesser SR.

MATERIALS AND METHODS

Chemicals

Diltiazem HCl (Reddy Pharma, Singapore) and hydroxypropylmethylcellulose 15,000cps (Colorcon, India) were obtained as gift samples. Lactose (BDH, England), magnesium stearate (Fluka, Germany), Gelucire 50/13 (Gattefosse, France), stearyl alcohol (BDH chemicals Ltd, England) and isopropyl alcohol (Merk, Germany)

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were purchased and used as such. Other chemicals used were analytical grade.

Preparation of HPMC-based sustained release tablets

Sustained release matrix tablets of diltiazem HCl were prepared using wet granulation method, by employing high viscosity grade of hydroxypropylmethylcellulose (HPMC) (formulations H1-H4, Table I). All the ingredients except magnesium stearate were weighed individually and sieved through mesh size No. 40 and were blended in a Kenwood mixer for 5 minutes and granulated with small amount of isopropyl alcohol and the wet mass so formed was sieved through mesh size No. 10 and dried at 60^{o}C for one hour in an oven (Memmert, Germany). The dried granules with moisture contents less then 5% were passed through mesh No. 12 and the fractions of granules retained on the sieve were discarded. Magnesium stearate passed through mesh No. 40 was finally mixed with granules and compressed separately using single punch machine (Emmy, Pakistan). The weight of granules were adjusted to 300 mg and compressed at fixed compression force.

Table I.- Tablet formulations of diltiazem HCl using HMPC.

Ingredients	Amount per tablet in formulation (%w/w)			
	H1	H2	H3	H4
Diltiazem HCL	30	30	30	30
HPMC	20	30	40	50
Lactose	47	37	27	17
PVP (K30)	2	2	2	2
Magnesium stearate	1	1	1	1

HPMC, hydroxypropylmethylcellulose; PVP, polyvinylpyrrolidone

Preparation of Gelucire-based sustained release capsules

Five lipid formulations G1-G5 (Table II) were prepared containing gelucire G50/13 and diltiazem in the ratio of 90:10, 80:20, 70:30, 60:40 and 50:50 respectively. Gelucire50/13 was first melted in a thermostatic bath by using hot plate magnetic stirrer with a temperature 20^{o}C above its melting point, for 30 min. Diltiazem with an accurate weight was then added and incorporated by continuous stirring at 500 rpm, for 1 hour. Once a uniform mixture was obtained, the resultant viscous matrices were filled into capsule using Pasteur pipette. The capsules were kept upright until the matrices solidified and were stored in amber bottles containing silica gel for 24 h at room temperature (25 ^{o}C) until being used for dissolution. Similarly, lipid formulations containing fixed proportion of diltiazem and different gelucire to stearyl alcohol ratios were also prepared (G6-G8, Table II).

Table II.- Semisolid formulations of diltiazem HCl using Gelucire with or without stearyl alcohol

Ingredients	Amount per capsule in formulation (%w/w)							
	G1	G2	G3	G4	G5	G6	G7	G8
Diltiazem HCL	10	20	30	40	50	30	30	30
Gelucire50/13	90	80	70	60	50	65	60	55
Stearyl Alcohol	-	-	-	-	-	5	10	15

In vitro *dissolution of solid and semisolid matrices*

In vitro dissolution of capsules and tablets was determined using the USP apparatus I, (basket method) and II, (paddle method) respectively (Pharm Test, Germany). The test was performed in 900 ml distilled water as the dissolution medium with the temperature maintained at 37.0±0.5°C, while the stirring speed was set at 50 rpm. Sample of about 5 ml each were collected at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 hours with an automated fraction collector (Pharm Test, Germany). At the end of 12 hours the matrix was pressed in the dissolution vessel to obtain homogeneous dispersion and the stirring continued for another 15 minutes. Samples were then collected and analyzed for drug content. All the samples were analyzed by diluting with distilled water at 240 nm using a UV-spectrophotometer (Shimadzu 1601, Japan). All the tests were run in triplicate and the values taken were averaged.

RESULTS AND DISCUSSION

Drug release from HPMC-based tablets

In order to achieve an optimum oral

formulation of diltiazem having desirable and sustainable release profile, sustained release tablets and capsules were prepared with high viscosity grade of HPMC and Gelucire50/13 (G50/13), respectively. Higher viscosity grade HPMC usually forms gel with greater strength whereas lower viscosity grade has lower gel strength (Nicole and Owen, 2004). High molecular weight HPMC was therefore, used as it forms a strong viscous gel on contact with aqueous media and may be useful in controlled delivery of highly water soluble drugs. In an attempt to prolong the release of drug, the concentration of HPMC in tablet formulations (H1-H4) was increased as shown in Figure 1. Apparently, drug release rate was decreased as the amount of HPMC was increased. In H3, HPMC and lactose at the given proportions provided comparatively linear release with a maximum of 80% of the drug released in 12 hours. At this time a

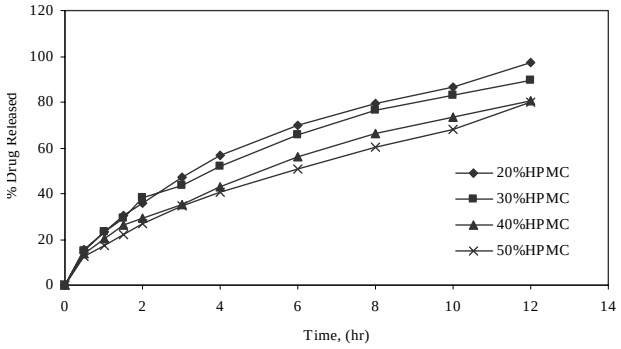

Fig. 1. *In vitro* release of diltiazem HCl from HPMC based tablet formulations (H1-H4).

swollen matrix was still floating in the dissolution medium. Faster release of drug from H1 was probably due to faster dissolution of highly water soluble drug from the core and its diffusion out of matrix forming the pores for entry of more media. As diffusion is related to transport of drug from the tablet matrix into the dissolution media, depending upon the concentration of polymer used therefore, by increasing concentration of HPMC in the tablet formulation lead to increase in diffusion path length and ultimately slower the drug release. Similarly, swelling of polymer was also dependent upon polymer concentration and increasing the concentration from 20% to 50% produced low swelling characteristic of matrix tablets that in turn resulted in slower release profile.

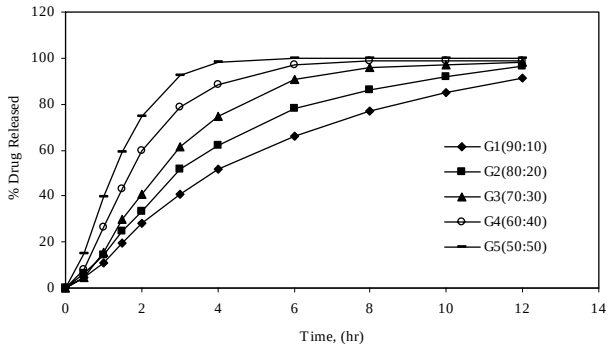

Fig. 2. *In vitro* release of diltiazem HCl from lipid matrices using a various Gelucire to drug ratios.

Drug release from Gelucire-based capsules

Several studies has been carried out on different Gelucires to investigate and relate the release properties to the dissolution of gelucire-based dosage forms (Kapocha *et al*., 1990; Prapaitrakul *et al*., 1991; Sutananta *et al*., 1995). Figure 2 shows the effect of G50/13 on in vitro release of diltiazem from lipid matrices (G1-G5). As the amount of diltiazem HCl increased in G5, a corresponding increase in the release rate was observed. The higher the level of G50/13 in lipid matrices the lower the active substances released indicating the most influential factor on release rate. A significant change in the release profile of formulations G1-G5 was noticed and it seemed that the time of dissolution is related to gelucire and its increasing amount used in these matrices. Instead of using greater amount of G50/13 in lipid matrix to prolong the release time, some parts were also replaced with hydrophobic additive, stearyl alcohol (SA). The release profile of lipid matrices (G6-G8) containing 5%, 10% and 15% SA in combination with G50/13 is depicted in Figure 3. It is apparent that the release rate of diltiazem was significantly reduced as the amount of SA was increased from 5%, to 15% and the percent drug released was about 97.56%, 89.52% and 81.28%, respectively. Therefore, higher the level of independent variable (SA) the lesser the active substances was released.

When the lipid matrices contacted water as dissolution media, there was no gelling of the polymer due to inability of the polymer to accommodate water uptake. The matrix system seemed to be disintegrated and dissolved completely after 12 hours. Similar release characteristics during a release study of carbamazepine from G50/13 have been reported (Galal *et al*., 2004). Hence, the drug release rate could be modified in a predictable manner by varying the amount of SA and might be possible to achieve nearly ideal drug release by using a proper combination of G50/13 and SA.

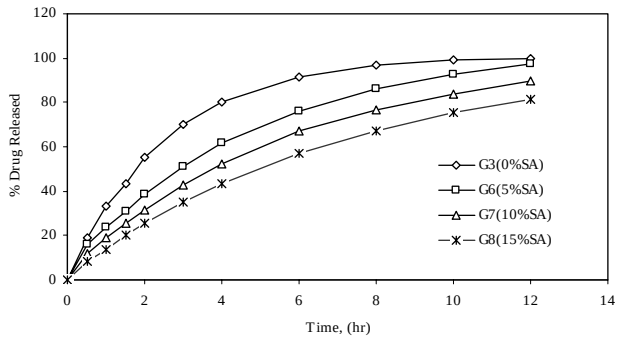

Fig. 3. Effect of stearyl alcohol (SA) on *in vitro* release of diltiazem HCl from Gelucire-based matrices.

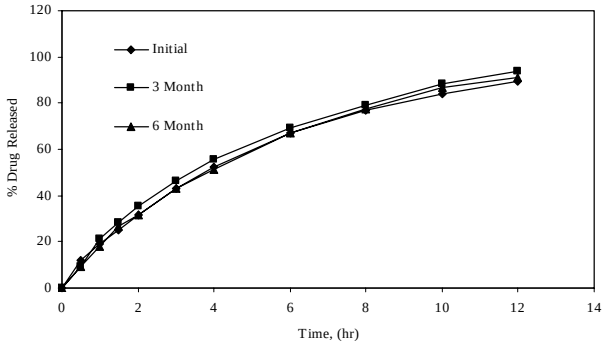

Fig. 4. Effect of aging on *in vitro* release of diltiazem HCl from lipid matrix capsule.

Ageing causes changes in the crystal structure of Gelucire, which is responsible for an increase in drug release (San-Vicente *et al*., 2000; Chauhan, 2004). The lipid matrix formulation (G7) as a function of aging was evaluated at room temperature. Figure 4 shows slight changes in the drug release rate with a higher loading of G50/13 (> 60%) and may cause negligible change in the biopharmaceutical parameter of lipid matrices for a period of six months. In addition, lipid matrix system (formulation, G8) was tested at three different pH values (1.0, 4.0 and 7.0). Apparently, the release profiles in different media were comparable and found to be statistically significant (Fig. 5). Diltiazem has slightly greater solubility in basic pH compared to acidic pH but these differences in the solubility do not affect the release profile significantly from the lipid matrix. Drug release from Gelucire 50/13 matrices took place principally by erosion, although the process was dominated by swelling and subsequent disintegration of the matrix, rather than simple dissolution of the base. Lipid soluble materials demonstrated predominantly diffusion-controlled release, while water-dispersible materials absorbed water and showed signs of swelling which led to erosion as an additional component of the release characteristics (Kopcha, 1990).

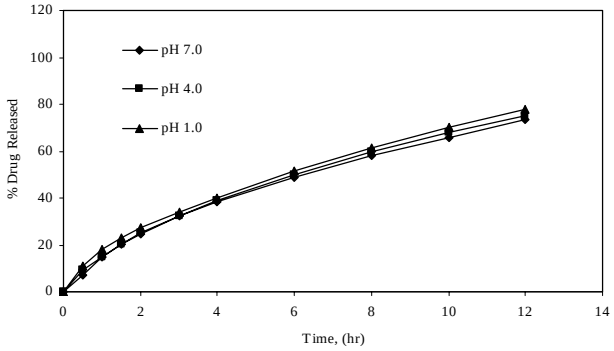

Fig. 5. Effect of pH *in vitro* release of diltiazem HCl from lipid matrix.

In vitro *comparison of HPMC-based and Gelucire-based matrices*

In order to get optimum sustained release formulation of diltiazem HCL, release data of tablet formulations (H1-H4) and capsule formulations (G1-G8) were fitted in zero order kinetic models. More linear and sustainable release profiles resulted from capsule formulation G8 and tablet formulation H3 compared to others. Therefore, release profiles of these formulations (H3 & G8) were compared

with commercially available sustained release product, Herbesser SR containing 90mg of diltiazem. No significant difference in the release rates of tablets or capsules (6.2 or 6.7 %/h) and Herbesser SR (6.9 %/h) was observed during 12 hours testing interval (Fig. 6). The f2 value obtained from drug release profiles of lipid or solid matrices versus reference was found to be greater than 90 indicating similarity in their release characteristics.

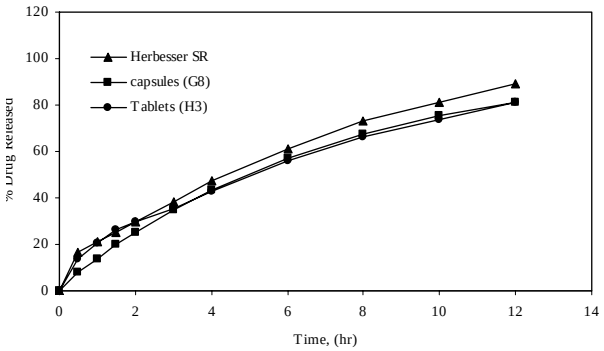

Fig. 6. *In vitro* comparison of two matrix systems with reference capsules, Herbesser SR.

CONCLUSION

Both lipid and HPMC based matrices produced remarkable decrease in drug release rate with increasing concentrations of lipid and HPMC, respectively. Greater reduction in the drug release rate was achieved by incorporation of hydrophobic substance stearyl alcohol in lipid matrix capsule. Moreover, drug release rate of both matrices was comparable with the reference product.

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