Suitability of Gelucire 50/13 for controlled release formulation of salbutamol sulphate

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Abstract: Gelucire 50/13 (G50/13) was assessed to develop controlled release formulation of salbutamol sulphate (SBL) a highly water soluble drug by semisolid matrix filling capsule technique. Drug release profiles of SBL release by using G50/13 and its blends with other hydrophilic or hydrophobic materials were investigated. Lipid matrix formulations prepared with increasing amount of polymer showed a substantial decrease in release rate of the drug while increasing drug amount in fixed polymer concentration did not significantly affect the release profile. Polyethylene glycol 6000 caused an increased water uptake resulting in fast erosion of the matrix whereas cetostearyl alcohol and stearic acid caused retardation in drug release. These findings confirm that a considerable amount of Gelucire is required alone or in combination with hydrophobic substances in order to sustain the release profiles of water soluble drugs. More linear profile was obtained by using matrix comprising Gelucire/stearic acid blend in more than 85% that was comparable to standard, Ventolin SR tablet. The test formulation showed a significant decrease at pH 1.0 and the drug release rate increased at high stirring speed. Moreover, short term stability of controlled release test formulation indicated slight increase in dissolution rate at high temperature.

Keywords: Semisolid matrix, gelucire, salbutamol sulphate, controlled release, stearic acid.

INTRODUCTION

Salbutamol sulphate has relatively shorter half-life (Gongora, 1991) requiring frequent dosing in the treatment of reactive airway disease as bronchodilator and its controlled release formulation may prolong the duration of action (Herna´ndez, 1996; 1997) decrease side effects, and improve therapeutic efficacy (Saleh, 1993).

Gelucire by compositions are inert semi-solid waxy materials that are amphiphilic in character and are available with varying physical characteristics. As to the chemistry of Gelucire 50/13 compositions, they are polyglycolized glycerides that are prepared by the alcoholysis reaction of natural oils with polyethylene glycols (PEG). They are mixtures of monoesters, diesters and/or triesters of glycerides of long chain (C_{12} to C_{18}) fatty acids, and PEG (mono- and/or di-) esters of long chain (C_{12} to C_{18}) fatty acids and can include free PEG. Gelucire compositions are generally described herein as fatty acid esters of glycerol and PEG esters or as polyglycolized glycerides. Gelucires are essentially characterized by their melting point and their hydrophilic-lipophilic balance (HLB). The higher melting point bases with greater proportion of lipophilic components are used as coating and matrix forming agents for sustained release formulations (Soberanez *et al*. 2011) while those having more hydrophilic components are more appropriate for sustained release (Nguyen *et al*, 2008) and bioavailability enhancers (Fini *et al*, 2005). Therefore, for immediate release, Gelucire with high HLB (55/18) and for sustained release preparations including nifedipine, ketoprofen, indomethacin and salbutamol with low HLB (54/02, 50/10, 48/09, 43/01) have been used (Dennis, 1990; Vial-Jato, 1990; Vial-Bernasconi, 1995; San-Vicente, 2000). Semisolid matrix formulations offer many advantages over conventional powder filled system that include excellent fill weight, content uniformity, the diminished dust or cross contamination, easier formulation of oily drugs, improved drug stability and easy modification of release rate by changing HLB value. In addition, the use of lipid matrix performs better in vivo due to absence of impurities and show high biocompatibility (Chauhan *et al*, 2004) and biodegradability.

Gelucire 50/13 is more hydrophilic due to higher HLB value compared to others such as 54/02, 50/10, 48/09, 46/07, 43/01 etc. and controlled release from this lipid matrix is not predictable for highly water soluble drugs. The present work was aimed to prepare controlled release semisolid matrices of salbutamol using Gelucire 50/13 alone or in combination with other hydrophilic or hydrophobic substances. In addition, the optimum semisolid matrix formulation was compared with a commercially available sustained release solid matrix product, Ventolin SR.

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MATERIALS AND METHODS

Materials

The following materials were used as received: salbutamol sulphate (FDC limited, Maharashtra, India), Gelucire 50/13 (Gattefossé, France), stearic acid (Merck, Germany), cetostearyl alcohol, potasium dihydrogen phosphate (BDH chemicals Ltd, England), disodium hydrogen phosphate (Sigma Aldrich, USA), polyethylene glycol 6000 (Merck, Germany).

Methods

Semisolid Matrix Capsules

Semisolid matrixes of salbutamol were prepared with changing ratios of Gelucire and drug (F1-F5, table 1) while blends were also prepared with hydrophilic and hydrophobic substances (F6-F11, table 2). As in most of the formulations (F1-F3, F6-F11), 8mg of drug per capsule was selected and considered to be ratio one while the amount of Gelucire taken as multiple of 8mg or one. In formulations F4 and F5, the amount of polymer was fixed (i.e., 8 multiplied by 25 is equal to 200mg) and the amount of drug was doubled or tripled. For preparation of all semisolid matrices, the weighed amount of Gelucire was heated in a beaker at 70ºC for 1 hour. After this the weighed amount of salbutamol sulphate was added to the molten Gelucire with continuous stirring using a hot plate stirrer. The drug was homogeneously mixed as the material was continuously stirred at 500 rpm and kept at a constant temperature of 70ºC for 30 minutes. After dispersion of drug, other hydrophilic or hydrophobic ingredients were added and mixed for another 30 minutes. The molten mixtures were then filled in the hard gelatin capsules No.2 with a pasture pipette, to a weight equivalent to 8 mg salbutamol and allowed to solidify at room temperature for 24 hrs. The fill weight of formulations F1 to F5 was variable (208-328mg) while the weight per capsule being the same (208mg) in all other formulations (F6-F11). As the body fills volume of shell No.2 is 0.37ml therefore, the above weight was easily filled. The filled capsules fulfilled the criteria for uniformity of dosage units as specified in British Pharmacopeia (2007).

In vitro dissolution studies

In vitro dissolution of all the capsules was determined using the USP apparatus I, basket method (PharmTest, Germany). The test was performed in 450 ml distilled water as the dissolution medium with temperature maintained at 37.0 ±0.5ºC, while the stirring speed was set at 100 rpm. Sample of about 5 ml each were collected at 0.5, 1, 1.5, 2, 3, 4, 6, 8 hours with an automated fraction collector (PharmaTest, Germany) after filtering through 10µm Sinter filter. At the end of 8 hours the matrix was pressed in the dissolution vessels to obtain homogeneous dispersion and the stirring continued for another 15 minutes. Samples were then collected and analyzed for drug content. The final reading after pressing the matrix represented the total amount of drug dissolved and was used to determine the percentage of drug released at different sampling intervals. All the samples were analyzed directly at 276 nm using a UV-spectrophotometer (Shimadzu 1601, Japan). All the tests were run in triplicate and averaged. The data obtained was analyzed on the basis of Higuchi equation and Langer-Peppas model to describe the release rates. In addition, release profiles of capsules were compared by similarity factor f_2 defined by the following equation is used to compare the difference of dissolution profiles between the commercial product and experimental formulation.

$$f_2=50\times\log\left[\{1+(1/n)\sum(Rt-Tt)^{2}\right]^{-0.5}\times100\}$$

Table 1: Semisolid matrix formulations of Salbutamol sulphate using Gelucire 50/13 (Drug and polymer ratios in brackets)

Ingredients (mg)	F1	F2	F3	F4	F5
Salbutamol SO_4	8(1)	8(1)	8(1)	16(2)	24(3)
Gelucire50/13	200(25)	240(30)	320(40)	200(25)	200(25)

Table 2: Semisolid matrix formulations of Salbutamol sulphate using Gelucire 50/13 in combination with hydrophilic and hydrophobic constituents (mg) (Drug and polymer ratios in is given in brackets)

Ingredients (mg)	F6	F7	F8	F9	F10	F11
Salbutamol SO_4	8(1)	8(1)	8(1)	8(1)	8(1)	8(1)
Gelucire50/13	192(24)	184(23)	192(24)	184(23)	168(21)	152(19)
Polyethylene Glycol	8(1)	16(2)	-	-	-	-
Cetostearyl Alcohol	-	-	8(1)	16(2)	-	-
Stearic Acid	-	-	-	-	32(4)	48(6)

where *n* is the number of dissolution sample times, and *Rt* and *Tt* are the individual percentages dissolved at each time point, *t*, for the reference and test dissolution profiles, respectively. The f_2 values greater than 50 (50–100) represents equivalence of the two curves.

Influence of pH and stirring speed

Formulation F10 containing Gelucire and stearic acid as shown in table 1, was selected for further studies. The release rate of salbutamol sulphate from the formulation was observed in different pH media. Three pH values namely pH 1.0 (0.1M HCl), distilled water and 7.4 (phosphate buffer, mixed) were used to note the effect of pH on drug release.

RESULTS

Three combinations of drug to Gelucire 50/13 ratio such as 1:25, 1:30 and 1:40 were therefore selected to note the effect of polymer on release rate of salbutamol sulphate. The effect of the drug was also investigated as the ratio or amount of the drug was increased to the fixed polymer contents in the formulation. Fig. 1 shows the effect of increasing amount of Gelucire on in vitro release of salbutamol sulphate from semisolid matrix (F1-F3). At lower ratio of Gelucire (F1) almost 100% of drug was delivered from semisolid matrix within 6 hours while at higher proportion (F3) about 60% of drug was released. The release profiles of semisolid formulations (F1-F3) were fitted to zero order, Higuchi and first order to obtain 'R' value and release rate constants whereas the value of 'n' indicative of release mechanism from Peppas model (table 3). The values of 'R' obtained from zero order were greater than Higuchi or first order kinetics. The value of '*k*' decreased in each kinetic model as the amount of polymer increased in these formulations indicating lower release rate. Moreover, the values of 'n' obtained from Pappa's model are in the range of 0.718 to 0.813.

Fig. 2 shows *in vitro* drug release from semisolid matrices using fixed amount of Gelucire with increasing amount of salbutamol (formulations F4-F5).

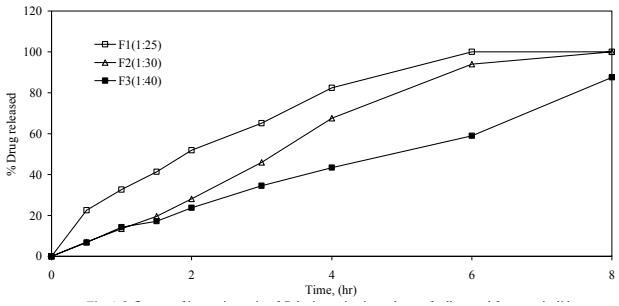

Fig. 1: Influence of increasing ratio of Gelucire on in vitro release of salbutamol from semisolid matrices.

Table 3: Values of release rate constant *k* and correlation coefficient *R* obtained from data of salbutamol sulphate release from formulations with various drug to Gelucire 50/13 ratios.

Model	F1	F2	F3
Zero order equation			
$k_{1\ (\%min^{-1})}$	18.793	17.821	14.798
R	0.992	0.997	0.998
Higuchi equation			
$k_{2\ (\%min^{-1/2})}$	37.194	35.314	29.439
R	0.934	0.936	0.941
First order Equation			
$k_{3\ (min^{-1})}$	0.893	0.926	0.862
R	0.947	0.885	0.879
Pappas Model			
n	0.813	0.753	0.718

No significant difference was obtained and the release profiles found to be comparable.

Incorporating a hydrophilic additive, polyethylene glycol 6000 in Gelucire-based matrix (F6-F7) as shown in fig. 3 resulted in an increase in dissolution rate of salbutamol sulphate Fig. 4 describes the possible modification of the salbutamol sulphate release from Gelucire-based matrix formulations in combination with cetostearyl alcohol (F8-

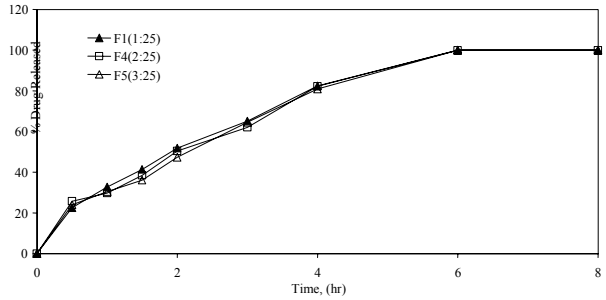

Fig. 2: Influence of increasing ratio of salbutamol sulphate on in vitro release using fixed amount of Gelucire.

F9). Some parts of Gelucire were also replaced with increasing proportion of stearic acid to modify the release rate of salbutamol sulphate. The release profile of semisolid matrices formulations (F10-F11) containing stearic acid is shown in the fig. 5. As the ratio of stearic acid was increased, a concentration dependent decrease in the release rate was apparent indicating more release retarding effect at higher concentrations.

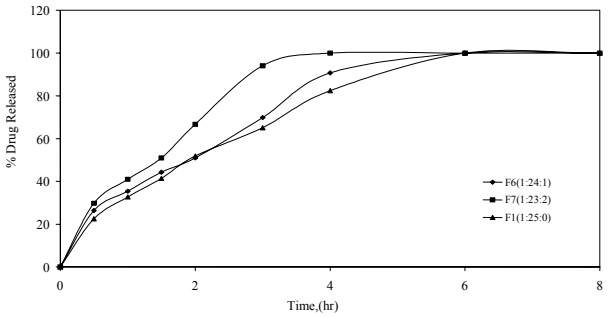

Fig. 3: Influence of increasing ratio of polyetylene glyco 6000 *in vitro* release of salbutamol.

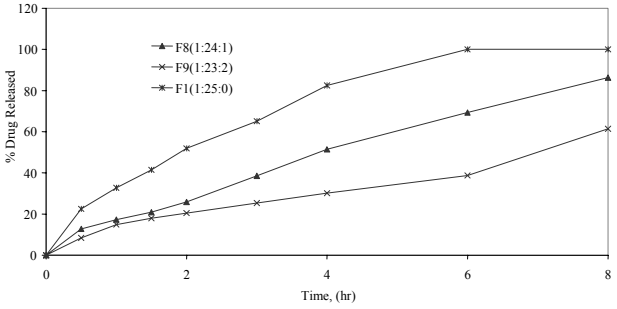

Fig. 4: Influence of increasing ratio of cetostearly alcohol on in vitro release of salbutamol.

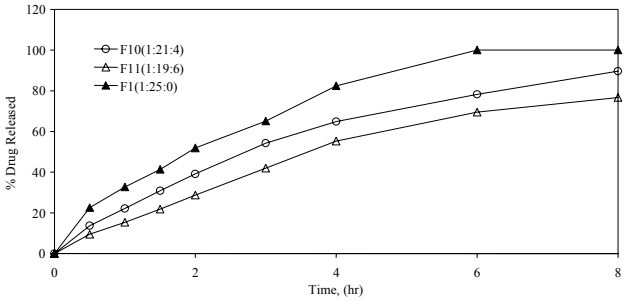

Fig. 5: Influence of increasing ratio of stearic acid on in vitro release of salbutamol.

From the above results, semisolid matrix formulation (F10) was selected for comparison with commercially available solid matrix, Ventolin SR containing 8 mg of salbutamol sulphate. The semisolid test matrix used for in vitro evaluation had almost same weight as that of reference tablets and drug contents of 10 capsules were determined by performing assay of individual capsule and found to be within the limits of content uniformity (85-115%). The dissolution profile of the test capsules with reference product, Ventolin SR 8 mg tablet (Fig. 6). Drug release rate of the test capsules seemed to be slightly lower than reference tablets during 6 hours testing interval while the remaining amount of drug released were similar in both the formulations. The extent of drug release from the test capsules was about 89% compared to 91% from Ventolin SR 8 mg tablet during the same time course of experiment. The *f*2 value of test versus reference preparations was found to be 54.32 greater than 50 indicating similar drug release profiles.

Fig. 7 shows the release profiles of salbutamol sulphate from the test formulations at two different pH values (pH 1.0 and pH 7.4). The rate of drug release in water and pH 7.4 were similar as the f_2 value being greater than 50. On the other hand the rate of drug release at pH 1.0 compared to water or pH 7.4 was lower. Fig. 8 shows the release profiles of salbutamol sulphate from the test formulations at different speeds. As the stirring speed was increased the disintegration of the test matrix was effected, indicating erosion of matrix at faster rate. The percentage drug released was about 52%, 90% and 100% at 50, 100, and 150 rpm respectively. The f_2 value obtained for 100 rpm vs. 150 rpm was greater than 50 and the f_2 value at 100 rpm vs. 50 rpm was less than 50.

The changes in the release rate of test matrix stored at 25°C and 40°C versus time were also studied. The in vitro results of test matrix at 25°C and 40°C have been depicted in figs. 9 and 10 respectively. The release profiles at 25°C were stable after six months and no change in the release rate was observed.

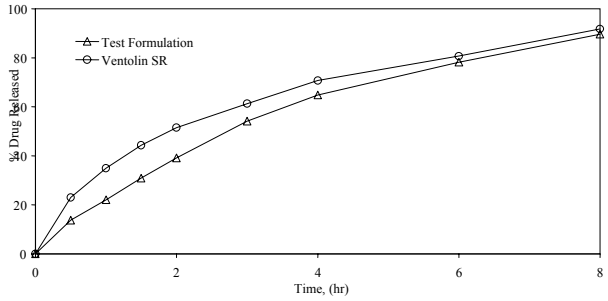

Fig. 6: *In vitro* release comparison of test formulation and reference product, Ventolin SR.

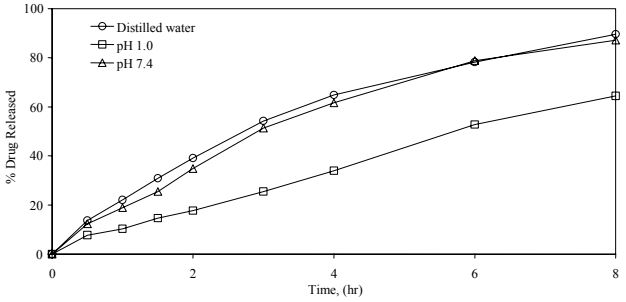

Fig. 7: Influence of pH on the in vitro release of salbutamol from Test formulation.

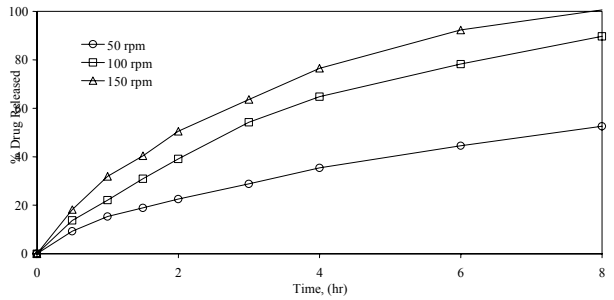

Fig. 8: Influence of stirring speeds on in vitro release of salbutamol from the test formulation.

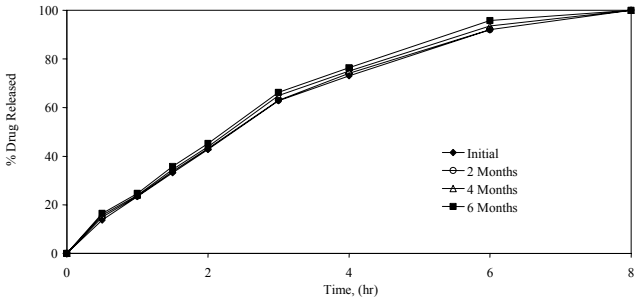

Fig. 9: Influence of aging on in vitro release of salbutamol from Test formulation after 2, 4 and 6 months storage at 25ºC.

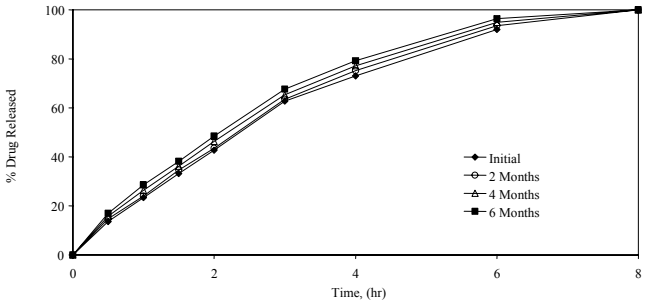

Fig. 10: Influence of aging on in vitro release of salbutamol from Test formulation after 2, 4 and 6 months storage at 40ºC.

At 40°C, the semisolid matrix converted into soft mass during storage that resulted in instability of the matrix and was unsuitable for long term stability studies (fig. 9).

DISCUSSION

The effect of increasing amount of Gelucire on release of salbutamol sulphate is shown in (Fig. 1). It seemed that the time of dissolution is related to the amount of polymer used in the matrices and the dissolution time was increased with the increasing proportions of Gelucire. When the matrix system contacted water, there was no gelling of the polymer due to inability of the polymer to accommodate water uptake. Instead the matrix system seemed to be eroded and dissolved completely after 8 hours. Similar release characteristics during a release study of carbamazepine from Gelucire 50/13 have been observed (Galal *et al.*, 2004).

Fig. 2 shows that salbutamol sulphate being freely water-soluble drug can modify the release rate by interacting with the integrity of the matrix system. But no prominent changes in drug release rates of F4-F5 were noticed due to its very small dose even at three different proportions in semisolid matrix whilst increasing amount of Gelucire had lead to changes in the release rate.

Addition of hydrophilic material like PEG 6000 accelerates the dissolution rate due to increase uptake of water that causes a rapid disintegration or erosion of the matrix system compared to formulations containing Gelucire without PEG (Muralidhar *et al*, 2011) (fig. 3). As water-soluble additive level increased, release also increased in contrast to similar level of salbutamol indicating slight structural changes in the matrix.

As shown in fig. 4 the incorporation of cetostearyl alcohol in Gelucire demonstrates that the percentage release of drug was reduced due to its poor wetting and the penetration of the dissolution fluid into the matrices. Similar behavior was observed when other hydrophobic material like stearic acid (Fig. 5) or a combination of cetostearyl alcohol and stearic acid was used in the Gelucire.

The formulation (F10) was compared with the standard Ventolin SR 8 mg Tablet. The two profiles were similar as the value of similarity factor *f2* was greater than 50. So this formulation was further studied for evaluating the effects of pH and stirring speed on the release behavior. At basic pH, release from these composite systems became more erosional in character compared to acidic pH, possibly reflecting partial hydrolysis of the ester-linked Gelucire-based matrices (fig. 7). The dissolution profiles (fig. 8) at stirring speed 150 rpm dissolution data were similar due to erosion and disintegration of matrix at higher speed. The dissolution data could not be matched at 50 rpm due to gradual swelling and erosion of matrix. 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, *et al.*, 1990).

It is well established that glyceride based products may exhibit aging effects, whereby a range of physical properties may change on storage of the bases which are sometimes accompanied by changes in the in vitro and in vivo release of drug from the dosage forms. The mechanism responsible for these changes has been

attributed to either the conversion of triglycerides to more stable polymeric forms (Liversidge, *et al*, 1981) or the conversion from amorphous to the crystalline state of the bases (Laine, *et al*, 1988). In the recent years several studies has been carried out on different Gelucires to investigate the release properties of these polymers and attempts have been made to relate the release properties to the dissolution from Gelucire-based dosage forms (Howard and Gould, 1987; Prapaitrakul, *et al*, 1991; Sutananta *et al*, 1995). Gelucire 50/13 also exhibit storage instability (Galal, *et al*, 2004) and exist in two principal melting forms (melting points 38°C and 43°C) that undergo transformation to the higher melting form on storage at 37°C. Scanning electron microscopy studies have indicated that system exhibit "blooming" with crystal formation on the surface. The dissolution rate increases particularly at higher temperatures (Khan and Craig, 2004). The results of this short term storage study, shown by Fig. 9 and Fig 10 are in good agreement with the reported study in which Gelucire (46/07) storage for one year at room temperature did not cause any change in the dissolution profiles of salbutamol sulphate whatever the capsule size (San-Vicente, *et al*, 2000). The authors also carried out studies of differential scanning calorimetry (DSC) of the melted mixtures of three different Gelucires used in formulation of lipid matrices with salbutamol sulphate in order to analyze the influence of aging. None of these mixtures showed any change in their calorimetric behavior depending on storage time. It seems that the influence of aging on the release of drug may be more prominent in the immediate release Gelucire than the slow release. Moreover, *in vivo* study of paracetamol from a lipid matrix before and after storage at different temperatures indicated that the extent of bioavailability could be maintained even when the lipid carriers were subjected to drastic environmental changes (Choy *et al.*, 2005).

CONCLUSION

Various lipid matrix formulations were prepared using Gelucire (50/13) alone and in combination with hydrophilic and hydrophobic materials. *In vitro* dissolution studies indicated that as the amount of Gelucire increased in the matrix the rate of drug release was decreased. The release rate kinetics of the Gelucire-based matrix system could be modified by the addition of hydrophilic or the hydrophobic agent. Polyethylene glycol 6000 tended to increase the release rate while hydrophobic agents, cetostearyl alcohol and stearic acid reduced the release rate. These findings confirm that a considerable amount of Gelucire is required alone or in combination with hydrophobic substances in order to sustain the release profiles of highly water soluble drugs while lesser amount of Gelucire would be required for poorly water soluble drugs to achieve similar release profile. Therefore, lipid matrix comprising Gelucire and stearic acid (F10) was found to be comparable with commercial product, Ventolin SR 8 mg tablet. A significant difference in the release profile was observed when the test matrix was tested in pH 1.0. Similarly the changes were apparent in the release rate at higher stirring speed compared to lower stirring speed. Storage at 25°C was found to be essential for stable release profile.

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