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Comparative Evaluation of Three Waxes of Different Hydrophobicities for Development of Matrix Tablets of Propranolol HCl

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ABSTRACT

The present work was aimed to develop a 24 hour modified release dosage form of model drug propranolol HCl using different waxes by hot melt granulation technique. Three waxes: stearic acid, cetostearyl alcohol and glyceryl behenate were used at 5%, 10%, 15% 20% and 30% concentration in matrix systems. Prepared formulations showed good tabletting characteristics. The effect of various waxes and their concentrations were studied on the release of the drug. The drug release profile from the wax matrices were tired to match with targeted dissolution profile (TDP). Matrix systems containing 30% stearic acid showed dissolution profile similar to TDP for initial hours and later the release was slower than TDP. In case of matrix system containing 30% cetostearyl alcohol, the drug release was within the TDP and with systems containing glyceryl behenate, propranolol HCl release was within TDP with 10%, 15% and 20% concentration. The release of drug was slower than TDP for matrix system containing 30% glyceryl behenate. The matrix system showing drug release within TDP followed non- Fickian diffusion.

Keywords: Matrix, stearic acid, cetostearyl alcohol, glyceryl behenate, targeted dissolution profile

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INTRODUCTION

Matrix tablets are most frequently used oral controlled release dosage form. Matrix forming material can be of hydrophilic, lipid, inert and biodegradable type; and the choice of material in dosage formulation is dependent on drug properties and desired drug release profile. In this system the drug reservoir is prepared by homogeneously dispersing drug particles in a rate controlling polymer matrix fabricated from either a lipophilic or a hydrophilic polymer[1]. Lipid based matrix drug delivery system have gain considerable interest due to factors such as better characterization of lipid excipients and formulation versatility[2]. Fats from various sources are used for formulation of drug delivery system. For controlling the drug release from the matrix, waxy polymers are used alone, or in combination with other waxes or in mixtures with other swellable polymers[3,4]. The hydrophobic and waxy materials used as matrix forming agents are potentially erodible and control the release of the drug through pore diffusion and erosion[5]. Various lipophilic materials studied as matrix formers are, carnauba wax, cetyl alcohol, hydrogenated vegetable oils, stearic acid and polyethylene glycols[6]. Lipophilic materials such as glyceryl behenate (Compritol® 888ATO). glyceryl palmitostearate (Percirol ® ATO5) , stearyl alcohol, paraffin wax, carnauba wax and bees wax have several advantages ranging from good stability at varying pH values and moisture levels to chemical inertness, safe application, and lower cytotoxicity in humans due to absence of solvents in the production process[7,8]. Barthelemy et al. [9] had investigated the use of glyceryl behenate as a hot-melt coating agent to prolong the release of theophylline. In their work, they were able to satisfactorily coat theophylline using glyceryl behenate and sustained the release over an extended period of time. The present study was aimed to study the drug release retadant effect of three different waxes that is stearic acid, cetostrearyl alcohol and glyceryl behenate on selected model drug , propranolol HCl. The once a day, wax matirx tablets of propranolol HCl were prepared using these three different waxes by melt granulation technique and drug release was studied for 24 h.

MATERIALS AND METHOD

Materials

Propranolol HCl was purchased from EMCO Industries Ltd. Hyderabad. Stearic acid was procured from Abitec corporation, Cetostearyl alcohol was purchased from Loba chemie and Compritol ATO 888 were procured from Gattefosse India. Lactose was gift sample from DMV International. Magnesium stearate was procured from Ferro USA. Colloidal silicon dioxide (Aerosil 200 Pharma) was received as gift sample from Evonik Technical Centre India. All other reagents used

for analysis were of analytical grade and procured from Merck India. Purified water IP was used wherever indicated.

Formulation of wax matrix tablets of Propranolol HCl

The wax matrix tablet of propranolol HCl was prepared preliminary by using individual concentration of waxes in the formulation and the granules were prepared using hot melt granulation technique. Melt granulation method is considered to be simple, efficient , less time and energy consuming and has the advantage it does not require the use of solvent for preparation of granule as the molten wax can function as binder or retardant[10]. The method in brief can be described as the drug and the diluent lactose were separately passed through 30# sieve and weighed. Waxes were weighed separately and all the excipients were taken in a glass beaker. The glass beaker was kept in water bath and the temperature was raised till the waxes were melted (till melting point of waxes). The molten mass was stirred continuously and maintained at that temperature for 15min. Then it was allowed to cool gradually to room temperature. The solidified mass was then milled and passed through 20# sieve. The granules obtained were then mixed with magnesium stearate and aerosil and were directly compressed on single station tablet punching machine using 12.5mm die punch. The composition of the formulation is listed in table 1 and 2. The concentration of waxes viz. stearic acid, cetostearyl alcohol and glyceryl behenate was kept as 5%. 10%, 15%, 20% and 30% w/w of total tablet weight.

Table 1: Composition of Preliminary batches of Propranolol hydrochloride using waxes

Batch/ Formula	FPS 1	FPS 2	FPS 3	FPS 4	FPS 5	FPC 6	FPC 7	FPC 8	FPC 9	FPC 10
Propranolol HCl	80	80	80	80	80	80	80	80	80	80
Lactose	385	360	335	310	260	385	360	335	310	260
Stearic acid	25	50	75	100	150	-	-	-	-	-
Cetostearyl alcohol	-	-	-	-	-	20	50	75	100	150
Glyceryl Behenate	-	-	-	-	-	-	-	-	-	-
Magnesium stearate	5	5	5	5	5	5	5	5	5	5
Aerosil	5	5	5	5	5	5	5	5	5	5
Total (mg)	500	500	500	500	500	500	500	500	500	500

Table 2: Composition of Preliminary batches of Propranolol hydrochloride using waxes

Batch/ Formula	FPG 11	FPG 12	FPG 13	FPG 14	FPG 15
Propranolol HCl	80	80	80	80	80
Lactose	385	360	335	310	260
Stearic acid	-	-	-	-	-
Cetostearyl alcohol	-	-	-	-	-
Glyceryl Behenate	20	50	75	100	150
Magnesium stearate	5	5	5	5	5
Aerosil	5	5	5	5	5
Total (mg)	500	500	500	500	500

Evaluation of compressed wax based matrix tablets of Propranolol HCl

Physical characterization of the matrix tablets

The hardness of 6 tablets from each of the prepared formulation was measured individually by using Monsanto hardness tester. Friability of tablets were determined using Veego Friabilator. The drug content for all formulations were determined using the tablet powder technique on 10 tablets. Each tablet was powdered and transferred to 100 ml volumetric flask. 10 ml of methanol was added to each flask and sonicated for 10 minutes then further 50 ml of 0.1 N HCl was added to the volumetric flask and further sonicated for 20 minutes. Finally the volume was made up to 100 ml with 0.1 N HCl and filtered. An aliquot of filtrate was suitably diluted with 0.1 N HCl to give a final concentration of 20ppm. The absorbance of this solution was measured at 292nm and compared to that of 20 ppm solution of Propranolol HCl working standard prepared in the same manner[11].

Drug Release study

The *In vitro* drug release from Propranolol HCl wax based matrix tablets were performed using USP type II dissolution test apparatus. The dissolution test was carried out for a total period of 24 hours. The dissolution medium comprised of 900ml of pH 6.8 phosphate buffer maintained at 37^{o} ± 0.5° C. The dissolution test was carried out at 50 revolutions per minute. An aliquot samples (10ml) were collected at predetermined time intervals and replaced with fresh medium to maintain constant volume. The samples were filtered and analyzed at 292 nm for propranolol HCl from matrix tablets by UV Spectrophotometer.

Release Kinetic studies

The drug release kinetic studies are useful tool to predict the mechanism of drug release of different formulations. Different mathematical models that is zero order, first order, Higuchi equations, Hixon Crowell cube root and Korsmeyer Peppas equations were applied to wax based matrix tablets of Propranolol HCl for describing the kinetics of drug release mechanism and the most suited was the one which best fitted the experimental results[12].

Zero order	$Q_i = Q_0 + k_o t$	(1)
First order	$\log C = \log C_0 - K_1 t/2.303$	(2)
Higuchi	$Q_i = k_2 t^{½}$	(3)
Hixon- Crowell Cube root	$Wo^{1/3} - W_t^{1/3} = k_h t$	(4)
Korsemeyer- Peppas	$Q_t/Q_\alpha = k_p t^n$	(5)

Where Q_0, Qt and Qα are the amounts of drug dissolved initially, at time t and at time α, (in most cases, $Q_0 = 0$), $C_0$and C are the concentrations of drug initially and at time t, $W_0$and W_t are the

amounts of drug in the pharmaceutical dosage form initially and at time t, and k_0, k_1, k_2, k_h and k_p refer to the rate constants obtained from the linear curves of the respective models.

RESULTS AND DISCUSSION

Physical characterization of Propranolol HCl wax matrix tablets

The physical appearance, hardness, thickness, weight variation , content uniformity and friability of all the tablets of different formulation were found to be satisfactory and are reported in table 3.The hardness of matrix tablets of all formulations were found to be between 6.2 to 7.5 kg/cm^2, friability was between 0.5 to 0.8 %. Thickness of all formulations were between 5.80 to 6.22 mm and drug content of all the formulations were between 98.37 to 100.09 %.

Table 3: Physical properties of Propranolol HCl wax matrix tablets

Formulations	Drug Content (%)	Thickness (mm)	Hardness (kg/Cm^2)	Friability (%)
FPS 1	98.56	6.17 ± 0.3	6.2 ± 0.4	0.78
FPS 2	99.32	6.10 ± 0.5	6.6 ± 0.2	0.61
FPS 3	100.01	5.82 ± 0.2	7.1 ± 0.3	0.50
FPS 4	99.82	5.91 ± 0.3	6.8 ± 0. 2	0.63
FPS 5	98.43	5.81 ± 0.1	7.5 ± 0.1	0.50
FPC 6	99.05	6.10 ± 0.2	6.4 ± 0.3	0.73
FPC 7	98.78	6.12 ± 0.4	6.7 ± 0.2	0.64
FPC 8	99.63	5.83 ± 0.1	7.1 ± 0.3	0.55
FPC 9	99.56	5.82 ± 0.1	7.3 ± 0.2	0.55
FPC 10	100.03	5.96 ± 0.4	6.7 ± 0.3	0.68
FPG 11	100.04	5.9 ± 0.3	6.2 ± 0.5	0.79
FPG 12	99.95	5.86 ± 0.3	6.9 ± 0.2	0.66
FPG 13	98.90	5.94 ± 0.4	6.7 ± 0.4	0.77
FPG 14	99.08	5.82 ± 0.1	7.5 ± 0.3	0.52
FPG 15	98.95	5.85 ±0.3	6.9 ± 0.3	0.74

Drug Release Study

Before performing the *in vitro* dissolution test of manufactured formulations, the targeted drug dissolution profile (TDP) was established. The TDP for propranolol HCl wax matrix tablets is listed in table 4. The values of the TDP are based on an average dissolution rate of 4% to 6.5 % per hour in order to achieve a 24 hour in-vitro release profile. The drug release profile of matrix formulations having different concentration of waxes such as stearic acid, cetostearyl alcohol and glyceryl behenate when used individually are shown in figure 1, 2 and 3. As shown in figure 1, 67.56% the drug got released from formulation FPS1 containing 5% stearic acid due to rapid erosion of the tablet. At 4 hr around 77.56% of the drug got release. This low concentration of stearic acid was unable to control and sustain the release of water soluble drug propranolol HCl for 24 h. Next trial was done with 10% of stearic acid and even this concentration of the wax was not

sufficient to control the release of drug and extend it to 24h. The reason for higher drug release could be high aqueous solubility of drug and excipient lactose used in the formulation which may form channel to diffuse the drug out[7]. With further increase in stearic acid concentration to 20%, matrix was able to control the release of drug but the drug release profile was faster than TDP. Hence the concentration of stearic acid in trial was further increased to 30% of the total tablet weight. Result obtained as can be seen in figure 1 indicates that initially the release of propranolol HCl was within the TDP of dissolution study but after 4th hour the release was much slower. The reason could be the high concentration of stearic acid could have formed a hydrophobic barrier on the drug during hot melt granulation technique but could also have formed a strong layer around the tablet due to fusing of wax into each other. And whatever the drug release was, could be because of the channel created by the presence of lactose. The highest drug release from stearyl alcohol formulations observed is in accordance with the findings of Karasulu et al[12] who explained that, on the basis of polymeric structure, stearyl alcohol was more convenient for drug diffusion. Moreover stearyl alcohol has a low melting and higher water absorption capacity than other wax polymers, allowing dissolution medium to penetrate the matrix system and resulting in faster drug release[13,14]. Cetostearyl alcohol is generally a viscosity increasing agent , chemically it is a mixture of solid aliphatic alcohol, mainly stearyl ($C_{18}H_{38}O$) and cetyl ($C_{16}H_{34}O$) alcohol[15]. The proportion of stearyl alcohol varies considerably but usually consists of about 50-70% stearyl and and 25-30% cetyl alcohol[15]. The aliphatic portions of long chain fatty alcohol imparts cetostearyl alcohol matrix with sufficient hydrophobicity and impedes wetting of matrix surface with dissolution fluid. Thus making cetostearyl alcohol a good release retardant for water soluble drug[16,17]. The drug release studied from formulation batches (FPC6 to FPC10) containing various concentration of cetostearyl alcohol (CSA) indicates that when concentration of CSA was low in matrix tablets that is 5 and 10% the wax was not able to retard the release of drug and in both the formulations FPC6 and FPC7 almost 70% of the drug got burst released in1h.With 15% and 20% of CSA in formulations (FPC8 and FPC9) the release got retarded but was comparatively faster when compared with TDP. But with 30% CSA in FPC10 the release was completely controlled and was within TDP for 12 h of dissolution testing but become slightly slower at 20h than the TDP. The reason for higher drug release from the formulations containing lower concentration of CSA could be attributed to physicochemical property of the drug and the level of the polymer. The low concentration of wax polymer is not able to control the release of highly water soluble drug. Drug particles present on the surface of matrix is initially released into surrounding media generating many pores which facilitates the release of drug. Moreover presence of lactose in formulation

could be giving synergistic effect in channel formation during drug dissolution. Compritol 888 ATO (glyceryl behenate) chemically is the mixture of mono, di and tri glycerides. It has a high melting point (60-80^{o}C). The formulation containing 5% of compritol 888 ATO was tested for in vitro dissolution, the formulation FPG11 showed 28.26% of drug release at 1h and 88.09 % of drug got released at 8h, indicating this low concentration of glyceryl behenate was not able to control the release of water soluble drug. The in vitro dissolution of formulation containing 10%, 15 % and 20% of the wax showed the release profile within the TDP. But when the concentration of glyceryl behenate in the matrix formulation was increased to 30% by weight of the tablet, the release of water soluble drug was sufficiently retarded. In formulation FPG15 containing 30% of wax polymer 0% drug got released in 1h and only 56.54% drug getting released at 12 h indicating a drastic retardation in release of the drug. In comparison to the other two wax materials that is stearic acid and cetostearyl alcohol, glyceryl behenate was able to retard the release of water soluble drug at low concentration level of 10% which either of the before mentioned wax materials was not able to do till 30% concentration by tablet weight. The reason for retardation of drug release at low concentration by glyceryl behenate could be due to high melting point of the polymer and more hydrophobicity compared to other two wax materials.

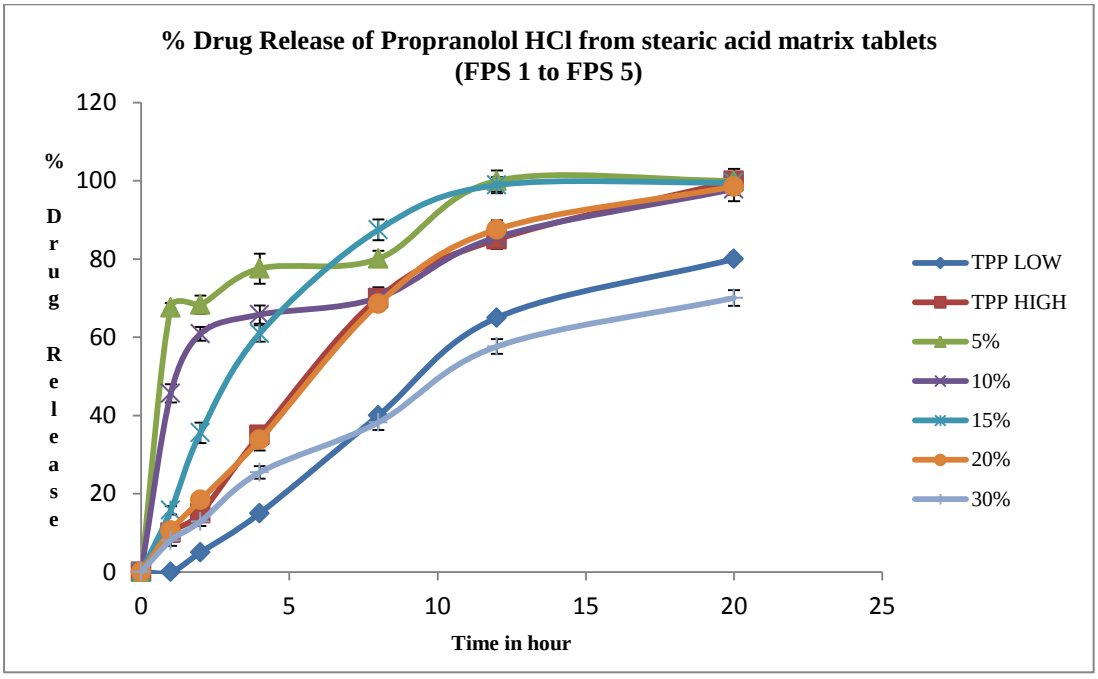

Figure1: 24 h drug release profile of Propranolol HCl from stearic acid matrix tablet

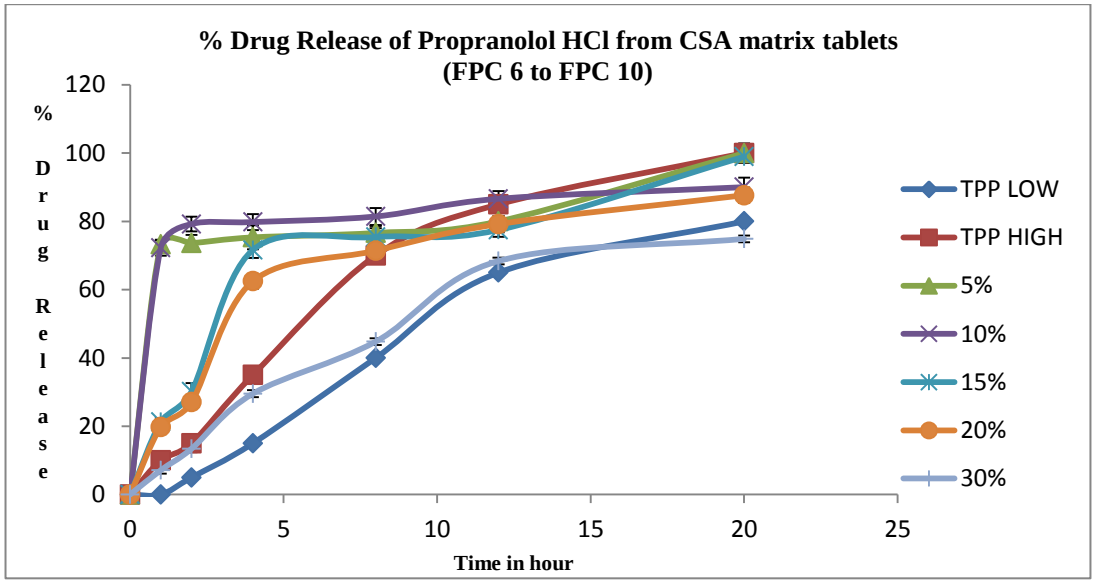

Figure 2: 24 h drug release profile of Propranolol HCl from CSA matrix tablet

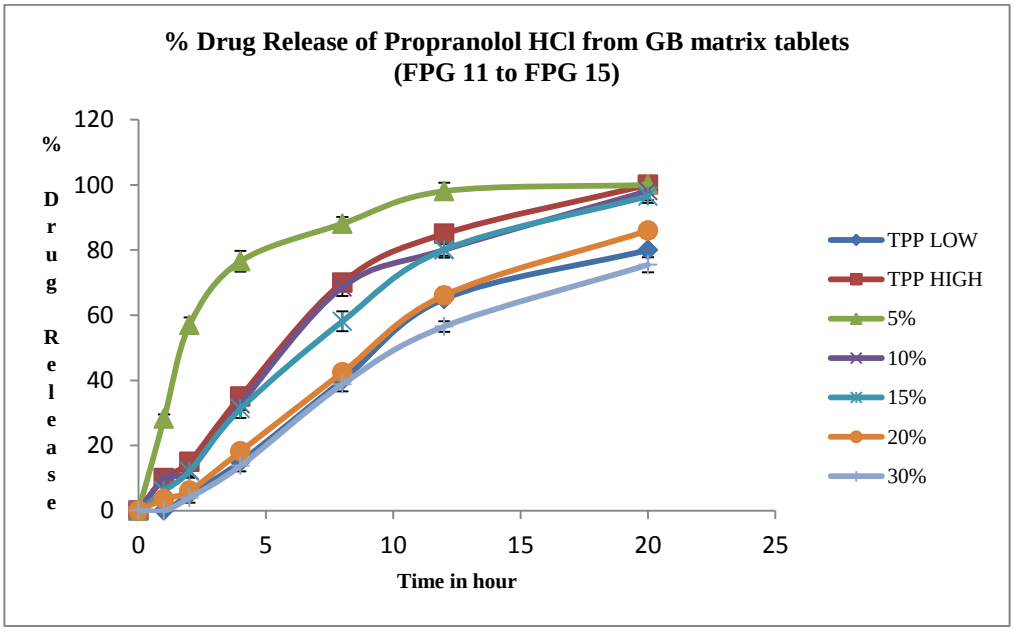

Figure 3: 24 h drug release profile of Propranolol HCl from GB matrix tablet

Table 4: Target Dissolution Profile

Time(h)	TDP Low (%)	TDP High (%)
0	0	0
1	0	10
2	5	15
4	15	35
8	40	70
12	65	85
20	80	100

Release kinetics

The drug release mechanism was understood by fitting the dissolution data obtained from wax matrix tablets to various rate kinetic models, the correlation coefficient values (R^2) for various formulations are listed in table 5. Wax matrix tablets containing stearic acid i.e. formulations FPS 1 to FPS 5 showed "n " values between 0.145 to 0.796. As formulation FPS4 was only slightly nearer to TDP, the n value analysis of this formulation showed that the drug release showed anomalous diffusion mechanism (n = 0.796). The drug released both by diffusion as well as swelling mechanism. Formulations prepared using cetostearyl alcohol as wax that is FPC 6 to FPC 10 showed "n" value between 0.065 to 0.819. Formulation FPC 10, having release profile within TDP showed n value of 0.819 indicating anomalous transport. Formulation prepared using glyceryl behenate showing drug release within TDP that is FPG 12, FPG 13 and FPG 14 showed n values of 0.860, 0.967 and 1.146. However the kinetic analysis of wax matrix showed a vast deviation in the values of release exponent "n", from which no clear inference could be made regarding the mechanism of drug release from such matrices. The mechanism of drug release from the wax matrices has been a matter of controversy since wax matrix tends to be crude and more heterogeneous as compared to other polymeric classes[18]. In some of the studies, it has been reported that the mechanism of release from wax matrices is through the pores and cracks in the matrix , from which the drug leaches out[19,20]. Other studies have reported that the drug release from wax matrices are diffusion controlled and their kinetics are best described by Higuchi model[21,22].

Table 5: Release rate kinetics of Propranolol HCl wax matrix tablets

Drug Release Kinetics						
Formulation	**Zero order**	**Higuchi**	**Hixon Crowell**	**First order**	**Peppas**	**n values**
FPS 1	0.5039	0.7496	0.8213	-	0.8846	0.145
FPS 2	0.6598	0.8734	0.7805	0.9389	0.9473	0.230
FPS 3	0.7574	0.9260	0.9988	0.9528	0.9100	0.617
FPS 4	0.9041	0.9579	0.9944	0.9787	0.9806	0.796
FPS 5	0.9495	0.9727	0.9910	0.9882	0.9912	0.748
FPC 6	0.4131	0.6326	0.3490	-	0.6097	0.081
FPC 7	0.3093	0.5610	0.4449	0.5814	0.9203	0.065
FPC 8	0.7508	0.9119	0.7777	0.9031	0.8903	0.514
FPC 9	0.7842	0.9218	0.8939	0.9216	0.9078	0.525
FPC 10	0.9118	0.9582	0.9884	0.9577	0.9763	0.819
FPG 11	0.6475	0.8794	0.9527	-	0.8571	0.395
FPG 12	0.9148	0.9529	0.9846	0.9621	0.9611	0.860
FPG 13	0.9398	0.9565	0.9945	0.9761	0.9778	0.967
FPG 14	0.9721	0.9281	0.9805	0.9853	0.9848	1.146

FPG 15	0.9691	0.9188	0.9833	0.9925	-	-

CONCLUSION

A wax matrix tablet can be successfully prepared using different waxes to obtain a 24h sustained release profile. All formulations prepared using hot melt granulation technique showed good tabletting properties like weight variation, hardness, thickness and friability. Formulations containing stearic acid and cetostearyl alcohol showed sustained release profile within TDP at higher concentration, whereas glyceryl behenate showed drug release within TDP at lower concentration of 10 to 20% of tablet weight. Higher concentration of glyceryl behenate showed retardation in drug release. Thus these matrix systems might be considered to sustain the drug release of water soluble drugs like propranolol HCl for 24 hours.

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