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A FEW WAXY MATERIALS LIKE WHITE BEES WAX (BW), CETYL ALCOHOL (CA) AND STEARIC ACID (SA) AS RATE REGULATOR FOR METFORMIN RELEASE FROM PEG-8000 BASED SUPPOSITORIES

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Abstract

In order to introduce *de novo* advanced anti-diabetic drug delivery system like polyethylene glycol (PEG)-8000 based suppositories containing metformin (a biguanide type of anti-diabetic drug) had been developed. Various successive formulations of PEG-8000 grade in combination with many other waxy materials like BW, CA and SA had been used to prepare suppositories.The dissolution studies of metformin in PEG suppositories containing different amount of BW, SA and CA in separate formulations were carried out in an "Electrolab Tablet Dissolution Tester USP XXIII TDT". The paddle rotation was set at 50 rpm and temperature was controlled at 37°C ± 2°C using 1 litre dissolution medium (pH 7.4). Waxy materials showed their fruitful rate controlling effect on metformin release. The kinetic constant, *k* values and diffusion coefficient, *D* decreased with an increase in waxy material in the system. The increasing *k* and *D* values indicated that the metformin release from the PEG-8000 based suppositories rate controlled drug release, where waxy materials might play a key role like as drug-release regulator. Metformin was successfully loaded up to 1600 mg on the basis of selection of comparatively better formulation and almost Case-II transport of metformin release was found from PEG-8000 based beeswax suppository system. Metformin released for a period of 10 h approximately. Metformin might be applied using this system once a day in stead of three times a day.

Key words: *Metformin, suppository, PEG-8000, diffusion coefficient, kinetic constant, NIDDM*

Introduction

Controlled Release Technology is being actively explored in the pharmaceutical industry due to therapeutic, economic, and commercial advantages [1]. So far it has been reported that many different types of controlled-release dosage forms have been developed to improve clinical efficacy of drug and patient compliance [2-3]. A number of methods and approaches have been used in their formulation and are well reviewed [4]. Products of this type have been formulated for oral, inject able and topical use, and include inserts for placement in the body cavities as well [5]. Suppositories can be formulated as one of these dosage forms. Suppository is the dosage form that is used in the rectal route. The rectal route has advantages for delivery of drugs with a narrow therapeutic index [6]. Besides SR oral dosage forms, SR rectal delivery forms are also used now-a-days for optimizing drug effects mainly in children and in elderly patients, a notion first recorded by Hippocrates. The rectal route of administration can be chosen both for local and systemic effects.

Anti-diabetic drugs are usually good candidates for the development of controlled release preparations particularly through the rectal route to reduce or eliminate the gastrointestinal irritation. Metformin hydrochloride (MH), an antidiabetic drug lowers both basal- and postprandial-elevated blood glucosein patients with non-insulin-dependent diabetes mellitus (NIDDM or type 2 diabetes) whose hyperglycemia cannot be satisfactorily managed by diet alone. Some high incidence of concomitant GI symptoms, such as abdominal discomfort, nausea, and diarrhea, may occur during the treatment [7].

Muyunck and Cuvelier (1991)[8] reported that frequent application of Polyethylene glycol (PEG) or pure triglycerides as suppository base induced damage resulting in ulceration and inflammation of the rectal mucosa. They further added that inclusion of monoglycerides or fatty acids in suppository base reduced rectal mucosa damage. Various grades of PEG have been already introduced like PEG grade-1000, 1500, 1540, 2000, 4000, 6000 and a combination of various grades such as 200:6000, 1000:4000, etc [9-14].

But a little work has been carried out using PEG grade-8000 for formulating suppositories. Therefore, it is our endeavor to disseminate our knowledge in Research Arena by formulating PEG-8000 based suppositories and also to incorporate different waxy materials like BW, CA and SA in the PEG-based suppositories separately in different percentages in order to investigate their regulating effect on metformin release.

Methods

Materials

Metformin.HCL was supplied by Squire Pharmaceutical Ltd. Pabna, Bangladesh.
White bees wax (WBW), Stearic Acid (SA), and Cetyl Alcohol (CA) (manufactured by BDH, UK) were supplied by Pharmaceuticals Laboratory, Rajshahi University, Bangladesh. PEG-8000 standard pharmaceutical grade used to prepare suppository base was originated by Fluka, Switzerland. Disodium hydrogen phosphate, Potassium Dihydrogen Phosphate and Sodium Chloride were purchased from BDH.

Preparation of Buffer

For the preparation of the phosphate buffer of P^H 7.4 salt of potassium dihydrogen phosphate and disodium hydrogen phosphate were used. For preparation of one litter 7.4 P^H phosphate buffer, 8 gm of sodium chloride, 0.19 gm of potassium dihydrogen phosphate, and 2.38 gm of disodium hydrogen phosphate were measured in a balance and taken in 1000 ml volumetric flask. The volume was adjusted by distilled water and made it 1 litter 7.4 P^H buffer was checked by P^H meter.

Determination of λ_{max}

λ_{max} varies from solvent to solvent either there is a blue or red shift. Hence a spectrum was carried out from 200nm to 400 nm for a dilute solution of Metformin in phosphate buffer saline P^H 7.4, prepared according to BP.

Preparation of working curve

To prepare a working curve for metformin HCl in PBS pH 7.4, various dilute solutions were made and UV light absorption was checked at λ_{max} of 233 nm. Then a standard curve was prepared

plotting absorbance data against drug concentration.

Five formulations of PEG-8000 based suppositories containing 0%, 5%, 10%, 15%, and 20% waxy materials for the bases of 2.5 gm moulds in total were prepared according to the following table-I. Drug was loaded little amount at this stage but later finding the better release curve bolus amount of drug had been added according to the formulation described in Table-II.

Stability testing of Suppository

A group of suppositories were kept at room temperatures and time to time the physical properties as well as potency were checked.

Measurement of drug entrapment

The measurement of drug entrapment has been done by declared weight of suppositories minus weight of prepared suppositories and the weight losses have been considered in case of drug. By this way, the net weights of drug remaining in the suppositories have been identified.

Dissolution rate studies

The dissolution studies of Met in PEG suppositories containing different amount of BW, SA and CA in separate formulations were carried out in an "Electrolab Tablet Dissolution Tester USP XXI TDT-06". The paddle rotation was set at 50 rpm and temperature was controlled at 37°C ± 2°C using 1 litre dissolution medium (pH 7.4). A ten-milliliter sample was taken at regular interval, which was immediately compensated for with the same amount of fresh medium previously heated to 37°C.

Analysis of drug content

The extent of release of metformin from each suppository was measured at 233-nm wavelength using Shimadzu UV-1200 Spectrophotometer. The absorbance data were processed by a computer and consequently the percent releases of the drug at different time were obtained. All the samples were performed triplicate and the data presented in the graphs were the mean values, where the coefficients of variation were within the limit.

Results and Discussion

Preparation of working curve

A standard curve was found with a slope of $y = 0.014649\,x$. Since the value of r^2 is 0.992 so there is an acceptable linearity between absorbance and drug concentration (Fig 1) and the slope value would the valid one to calculate the drug concentration during cumulative dissolution.

Preparation of suppositories and drug loading

PEG-8000 based suppositories were successfully prepared with various percentages of waxy materials, where Metformin 50 mg was also successfully loaded (Fig 2, 3 and 4). Thereafter finding a better release pattern and release regulator, metformin was loaded successfully up to an amount of 1600 mg (Fig 4). Keeping 1600 mg metformin loaded in the suppositories various PEG/waxy material ratios were also introduced (Fig 5). Fig. 2 indicates 5%, 10%, 15% and 20% bees wax combination PEG-based suppositories from 1 to 4, respectively. Fig. 3 indicates 5%, 10%, 15% and 20% cetyl alcohol combination PEG-based suppositories from 5 to 8, respectively.

Fig. 4 indicates 5%, 10%, 15% and 20% stearic acid combinations PEG-based suppositories from 9 to 12, respectively. Fig.5 PEG-based suppositories containing constant amount of bees wax (600mg) and variable amount of drug (1=100, 2=200, 3=400, 4=800 and 5= 1600 mg, respectively).

Kinetic studies

The results of the dissolution studies of Metformin from the PEG-based suppositories containing various amounts of BW, SA and CA were discussed in Figure 7, Fig 8 and Fig 9 as well as in Table-III. Table III showed detail kinetic profiles of waxy material in PEG based suppositories. Figure 10 and Figure 11 explained a little around drug loading and waxy material combination keeping former constant in later case and *vice versa*. The kinetic profiles such as diffusion exponent, kinetic constant, release rate, diffusion coefficient all were calculated from the figure 7, 8, and 9, respectively.

Figure 8 showed the release behavior of metformin from stearic acid/PEG-8000 based suppositories, where stearic acid can act as release modulator. It had been observed that release pattern decreased when SA concentration was increased. Figure 9 showed the release behavior of metformin from that of bees wax combination PEG based suppositories. Figure 10 showed the effect of drug loading on the metformin release. Up to 1600 mg of metformin was successfully loaded and the release was Higucian[15] in all the cases.

Release rate was faster when drug loading increased rationally (Table IV) keeping bees wax amount constant. The release fashion was found almost 0 order or Case-II transport governed pattern (r^2 0.98-.99, with diffusion exponent 0.99). 1600 mg of metformin could be successfully loaded without any physical and chemical hazards (Figure 5). Keeping drug loading constant at 1600 mg beeswax combination changed and release pattern changed to a Higuchian governed fashion (Table III). The release rate decreased with increasing beeswax, where drug was kept constant at 1600 mg.

Korsmeyer *et al.* and Peppas presented a simple, semiempirical equation, which can be used to analyze data of controlled release of water-soluble drugs from the polymers[16,17]. The general form of this equation is:

$$M_t/M_\infty = k\, t^n \quad \ldots\ldots\ldots \quad \ldots. \quad \ldots\ldots (1)$$

Where, M_t/M_∞ is the fractional release, k is the kinetic constant, and n is the diffusion exponent, characteristic of the mechanism of diffusion release. It would be the value of 1, when there is a zero order or Case-II transport process in the system.

Diffusion exponent, n

When log M_t/M_∞ was plotted against log t, the values of diffusion exponent, n were found out for the suppositories [18] of different system with correlation coefficient, r^2 = 0.993-0.999 (Table III). According to the mathematical modeling [19] for slab, sphere, cylinder or matrix disc, the values of diffusion exponent, n=1, when release process is exactly zero order process, a Case-II transport and $0.5<n<1$ would be a Non-Fickian diffusion, where $0.43 \leq n \leq 0.5$ is known as Fickian diffusion for the first 60% to 70 % release. The values for the diffusion exponent indicated a Non-Fickian diffusion in a critical analysis of data rather than a case-II transport (Table III).

Diffusion co-efficient, D

The diffusion co-efficient, D was found out for 60% release of the early time approximation of Fick's second law of diffusion according to the following equation [20]:

$$M_t/M_\infty = 1-[4/(2.405)^2] \exp[-(2.405)^2 D\, t / r^2] \quad \ldots\ldots\ldots \quad \ldots\ldots\ldots \quad (2)$$

Where D is the diffusion coefficient and r is the radius of the suppositories (Radius = 0.5 cm). The D values of metformin from the suppositories decreased with increasing the waxy materials. It provides the theme of increasing hydrophobic part of the system, which impeded penetration of water molecules inside the system caused such a decrease in D (Table III). This value dramatically controlled with inclusion of BW than those of SA and CA. Increasing BW concentration resulted in drastically lower value of diffusion coefficient.

Kinetic constant, k

The kinetic constant, k was found out from the simplified equation, Eq. (1). It is a kinetic parameter, which indicates the nature of interaction between the macromolecular network system of the polymers, and drug inside the system. The k values like diffusion coefficient decreased with an increase in waxy material in the system (Table III). The increasing k and D values indicated that the metformin release from the PEG-8000 based suppositories rate controlled drug release, where waxy materials might play a key role like as drug-release regulator.

Release rate

In Table-III it is observed that release rate (% release/$min^{-1/2}$, obtained from the slopes of figure 7, 8 & 9) decreased with the increase of the waxy material in the system, which concorded with the D and k contribution. It had been observed that release rate was promptly controlled in BW other than those of CA and SA. Considering release rate, D and k values as well as release fashion 15% BW had been selected for bolus drug loading formulation and also for BW-PEG combination formulation keeping bolus drug content constant.

Conclusion

To explore the use of PEG-8000 grade in suppository preparation, various successive formulation of this grade had been possible in combination with many other waxy materials like BW, CA and SA. Waxy materials were used to find out their regulating effect on metformin release and these materials showed their fruitful rate controlling effect on metformin release. Selecting the better formulation of PEG-beeswax combination, drug was successfully loaded up to 1600 mg, which showed

almost Case-II transport of metformin release from such a suppository system. This indicated a great impact on metformin dosage regimen, resulting dose frequency to once a day rather than *ter in die*. In this way *Diabetes mellitus,* especially NIDDM could be promptly managed with such kind of dosage form or with other combination of active drug like pioglitazone, sulfonyl urea etc in this dosage form, where dose dumping possibility might be abolished totally. Prompt anti-diabetic effect from such a system might be introduced as a *de novo* device in advanced drug delivery system.

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Table 1: Formulation of PEG-based suppositories with the addition of waxy materials
Preparation of suppositories and drug loading

Formulation No. (x 3)	Metformin (mg)	PEG (mg)	BW (mg)	SA (mg)	CA (mg)
FM-1	50.0	2450	0.0	0	0
FM-2	50.0	2325	125	--	--
FM-3	50.0	2200	250	--	--
FM-4	50.0	2075	375	--	--
FM-5	50.0	1950	500	--	--
FM-6	50.0	2450	--	125	--
FM-7	50.0	2325	--	250	--
FM-8	50.0	2200	--	375	--
FM-9	50.0	2075	--	500	--
FM-10	50.0	2450	--	--	125
FM-11	50.0	2325	--	--	250
FM-12	50.0	2200	--	--	375
FM-13	50.0	2075	--	--	500

Table-II: Formulation of drug loading and bees wax –PEG combination

Drug Loading	Beeswax changing	Metformin (mg)	PEG-8000 (mg)	Beeswax (mg)
F-1	-------	100	3300	
F-2	--------	200	3200	
F-3	---------	400	3000	*600 in each formulation*
F-4	---------	800	2600	
F-5	---------	1600	1800	
-------	F-1	*1600 in*	800	600
-------	F-2	*each*	650	750
-------	F-3	*formulation*	500	900

* Total yield: Practical weight of suppositories/Theoretical weight x 100

Table III. Kinetic profiles of metformin release from the PEG/BW, PEG/CA, and PEG/SA suppositories

PEG-8000 Combination			*Higuchian Release Rate (%release/√min)*	Diff. Coeff. (D,.x10^{-4} cm^2min^{-1}) *$0.3 \leq M_t/M_\infty \leq 0.75$*	*Diffusion Exponent (n) for $0.6 \leq M_t/M_\infty \leq 0.7$*	*Kinetic Constant (.x 10^{-3} % min^{-n}) (k)*	*Corr. Coeff. (r^2)*
BW	*CA*	SA					
5	-	-	6.35	3.37	0.57	45.44	0.995
10	-	-	5.69	2.73	0.79	15.7	0.997
15	-	-	1.13	0.115	0.78	1.41	0.986
20	-	-	0.85	0.013	0.69	1.76	0.993
-	5	-	3.96	1.132	0.55	28.0	0.997
-	10	-	2.76	0.571	0.51	25.9	0.999
-	15	-	2.74	0.47	0.61	13.04	0.998
-	20	-	2.59	0.43	0.64	10.78	0.999
-	-	5	6.788	2.71	0.745	14.8	0.987
-	-	10	4.889	1.84	0.733	13.36	0.999
-	-	15	3.988	1.02	0.676	12.95	0.999
		20	2.964	.0214	0.676	10.68	0.997

Table IV: Effect of drug loading and beeswax-PEG combination on metformin release

Drug/waxy material parameter		Corr. Coeff.		Release rate
Drug loading Variable (mg)	Waxy material Variable (mg)	0' Order	Higuchi	
100	Bees wax 600	0.99	0.975	3.597
200	in each	0.98	0.991	4.288
400	formulation	0.99	0.986	5.541
800		0.99	0.978	7.155
1600		0.99	0.989	8.016
	600	0.98	0.992	7.564
1600 in each	750	0.93	0.975	5.738
formulation	900	0.97	0.983	5.497

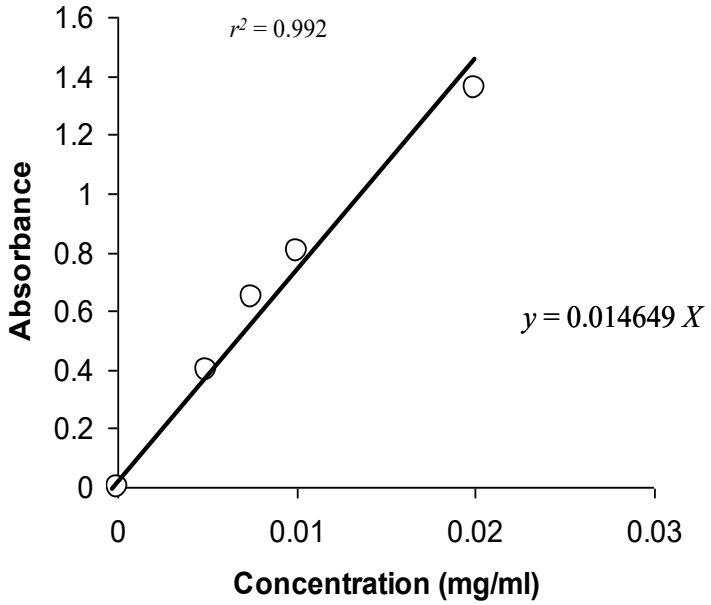

Figure 1: *Working curve for metformin*

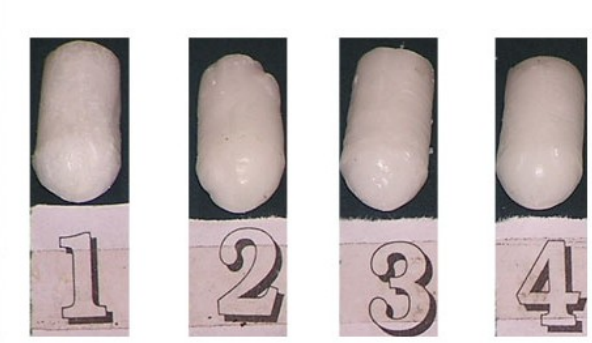

Figure 2: Metformin loaded suppositories containing Beeswax 5% (1), 10% (2), 15% (3) and 20% (4)

Figure 3: Metformin loaded suppositories containing Cetyl alcohol 5% (5), 10% (6), 15% (7) and 20% (8)

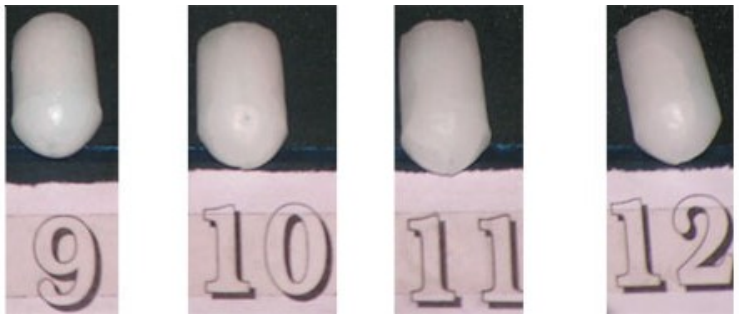

Figure 4: Metformin loaded suppositories containing Stearic acid 5% (9), 10% (10), 15% (11) and 20% (12)

Figure 5: PEG-based suppositories containing constant amount of bees wax (600mg) and variable amount of drug (1=100, 2=200, 3=400, 4=800 and 5= 1600 mg, respectively).

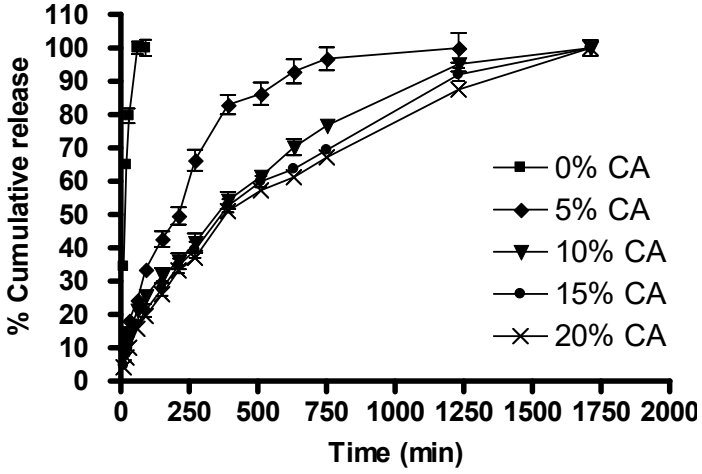

Figure 6: Effect of CA on metformin release from PEG-8000 based suppositories

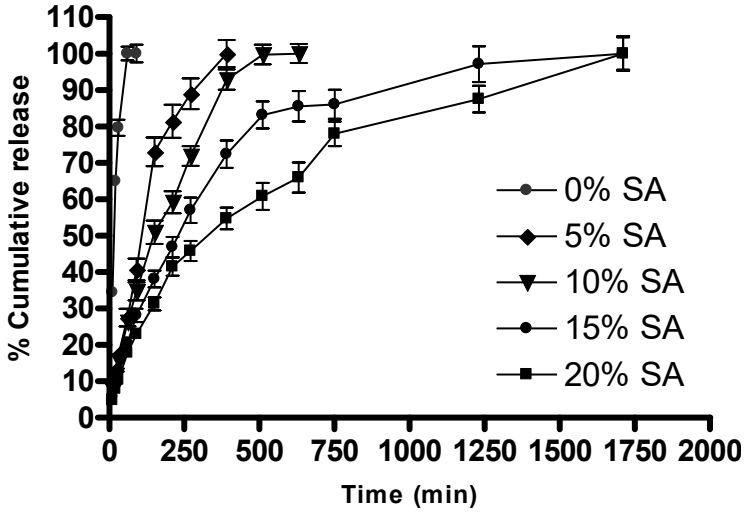

Figure 7: Effect of SA on metformin release from PEG-8000 based suppositories

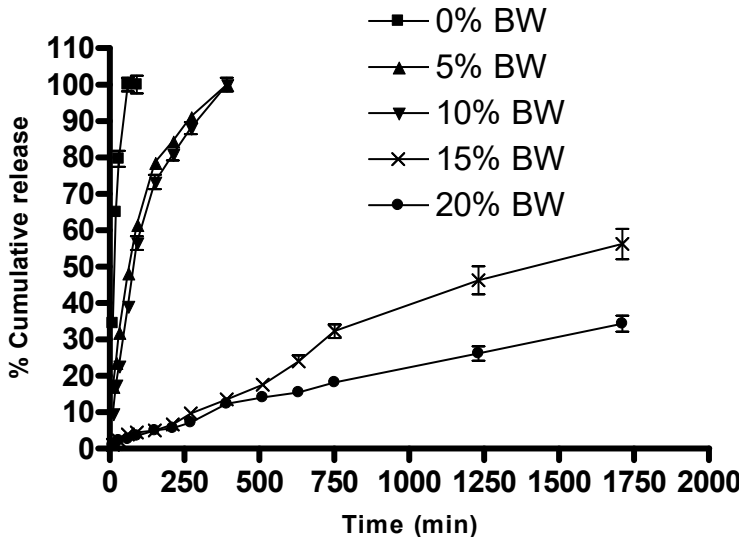

Figure 8: Effect of BW on metformin release from PEG-8000 based suppositories

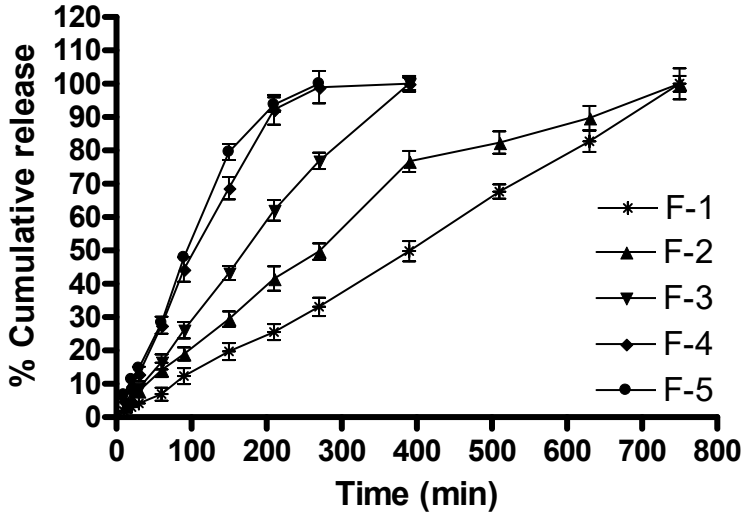

Figure 9: Effect of drug loading on the metformin release from PEG based suppositories. F-1, F-2, F-3, F-4 and F-5 are the metformin content of 100 mg, 200 mg, 400 mg, 800 mg and 1600 mg, respectively.

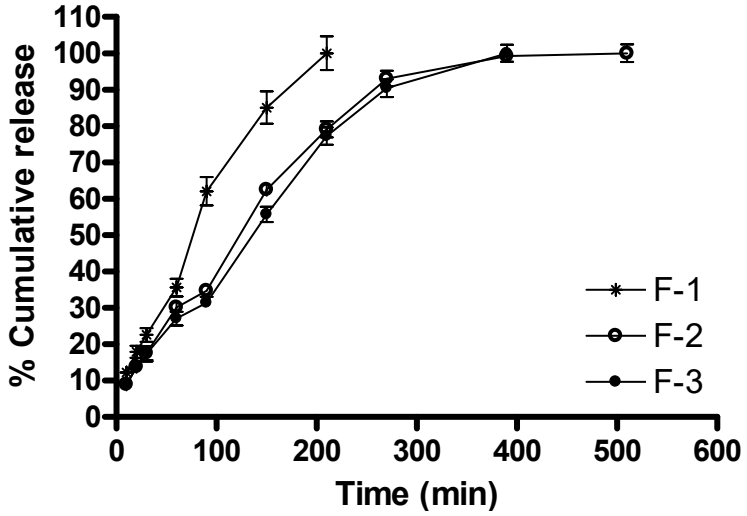

Figure 10: Effect of PEG/waxy material combination keeping drug loaded constant at 1600 mg. F-1, F-2 and F-3 contain the Beeswax 600 mg, 750 mg and 900 mg, respectively.