



Research Article

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Preparation and evaluation of Levodropropizine suppositories

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ABSTRACT

The objective of this work was to prepare and evaluate the effects of various of hydrophilic (polyethylene glycol and poloxamer) and hydrophobic (Witepsol H15 and Novata BCF) bases on in-vitro dissolution profiles and release characteristics of Levodropropizine from suppositories, in order to get immediate-release formula. Suppositories containing 60 mg of Levodropropizine along were prepared using the fusion method technique. All suppositories were evaluated for physical characteristics, in-vitro drug release, kinetic models and mechanisms. Drug dissolution profiles were different from those bases which were attributed to natural and characteristics of base that was used. The effect of incorporating different concentrations of non-ionic surfactants (Tween 80) on the release rate of the drug from Witepsol H15 and Novata BCF, was investigated. Results showed an enhanced release at low surfactant concentrations. A very fast 100% drug release was achieved when the drug was incorporated as an aqueous solution in Witepsol H15. Poloxamers have mucoadhesive properties hence they adhere to rectal mucosa, and are characterized by low toxicity and good compatibility with other substances, they also provide good drug release characteristics by producing solid dispersions with drug which enhances the solubility and dissolution rate of Levodropropizine. The formula of poloxamer188/propylene glycol, PG,(70/30) gave the best results in physicochemical tests which released the drug completely in the first 10 minutes of dissolution test .

Keywords: Levodropropizine, non-ionic surfactants, solid dispersions, Poloxamer 188

INTRODUCTION

Levodropropizine(S(-)-3-(4-phenyl piperazin-1-yl)-propane-1,2-diol), the levo isomer of dropropizine is a peripheral inhibitor of sensory C-fiber acceptors located in the lungs. Levodropropizine is a non-opioid compound which has been recognized to be an effective antitussive drug against cough associated with different lung pathologies, but without important central side effects and more favorable benefit/risk profile when compared to dextromethorphan so it is considered as a safe and effective option for dry cough treatment in children[1]. Levodropropizine is available in the market as syrup and Tablets[2,3]. There is no information related to the manufacturing of Levodropropizine in the form of suppositories. The rectal route for drug administration is preferred in children[4] because of reduced side effects, such as gastrointestinal irritation, and to avoid both displeasing taste and first pass effect. The release properties of suppositories depends on the physicochemical properties of the drug, suppository base and formulation adjustment[5].

This study aims to prepare Levodropropizine suppositories for children and to optimize its release characteristics from different suppository bases . Solid dispersions have been used to enhance the dissolution rates of poor water-soluble drugs with a hydrophobic drug. The carrier must be hydrophilic to facilitate fast dissolution of the

therapeutic agent into the aqueous medium of the gastrointestinal tract[6]. In this paper, solid dispersions of Levodropropizine with various polymer carriers are studied .

EXPERIMENTAL SECTION

1. Materials:

The following materials were used: Levodropropizine (Shanghai Soyoung Biotech .Inc), Polyethylene glycol 400,1000, 1500,and 4000 (Riedel-De HaenAgseelze-Hannover ,Germany), Witepsol H15(Dynamit Nobel, Leverkusen, Germany), Novata BCF (Lotte chemical, Korea), Tween80 (Riedel-De HaenAgseelze-Hannover, Germany), Poloxamer 188 (Sigma-Aldrich, Germany) Potassium phosphate monobasic (Sigma-Aldrich, Germany), Sodium Hydroxide (Avon chem., UK).

2. Preparation of Levodropropizine suppositories:

Children Levodropropizine suppositories containing 60 mg of drug were prepared by melting and molding technique[7] using different fatty and hydrophilic bases .

The value of f which shows how much base is displaced by a unit weight of an API, was calculated using the following equation[8]:

$$f = \frac{100(E-G)}{G*x} + 1$$

where E is the weight of the blank suppository containing only base, G is the weight of the suppository containing an API in a known concentration, and x is the API content of the suppository in weight percentage.

The suppository base weight was calculated by the following formula[8]:

$$Tm = E - \sum_{i=1}^n f_i * s_i$$

where Tm is the suppository base to be weighed, E is the calibration constant of the mold, f is the displacement factor of the each component and s is the weight of the each component. The suppository base was melted and then the drug was added. Homogeneous dispersions were formed by stirring continuously and then molded in a metal mold (1 ml capacity). Suppositories for adults are usually 2 mL and for children 1 mL [9]. The selected fatty bases were Witepsol H15, Novata BCF. Hydrophilic bases were mixtures of PEG400/PEG1500/PEG4000/Propylene glycol and mixtures of poloxamer188 /propylene glycol. Moreover, Tween 80 was added to Witepsol H15 and Novata BCF suppositories bases(Table 1). All suppositories were kept in aluminum paper because of the drug's sensitivity to light[10], and stored in a desiccator at room temperature for 24 h before test.

Table1: Codes, composition of solid suppository formulations

Code	Suppository composition
F1	PEG1500 47.5%+PEG4000 47.5%+PEG 400 5%
F2	PEG4000:45%+PEG1500:45%+PEG400:5%+PG:5%
F3	PEG 1500 44%+PEG 4000 44% +PEG 400 5%+PG 7%
F4	witepsol H15 100%
F5	wetipsol H15 95%+tween80 5%
F6	witepsol H15 90%+tween80 10%
F7	Novata BCF 100%
F8	Novata BCF 95%+tween 80 5%
F9	Novata BCF 90%+tween 80 10%
F10	Poloxamer 188 100%
F11	Poloxamer188 70%+PG30%
F12	Poloxamer18850%+PG50%

3. Evaluation of the prepared Levodropropizine suppositories:

3.1. Weight variation:

Twenty suppositories were weighed individually and the average weights were determined. No suppositories should deviate from average weight by more than 5% except two, which may deviate by not more than 10% [11].

3.2. Content uniformity:

Ten suppositories were randomly selected from each formula and assayed individually for drug content. The suppository was melted with gentle heating in a water bath in the presence of 50 mL phosphate buffer solution, pH 7.2. The volume was adjusted to 250 mL with phosphate buffer. The flask was disturbed on an ultra sound water bath (PHYLO, USH-10D Italy) at 37°C for 4 h. After ten-times dilution and filtration, the UV absorbance of the solution was measured spectrophotometrically (Cary 500 Scan-UV-Vis-NIR spectrophotometer EL02015161) at λ max 240 nm against a blank solution prepared by treating plain suppositories in the same manner [7].

3.3. Hardness:

Hardness was determined at room temperature (about 25°C) using a hardness tester (ERWEKA-APPARATEAU-G.m.b.H 19359) [7].

3.4. Disintegration test:

The disintegration test determined whether the suppositories disintegrate within prescribed time. Each apparatus is placed in a beaker with a minimum capacity of 4 liters filled with water. The beaker is fitted with a slow stirrer and a support that holds the apparatus vertically 90 mm below the surface of the water so that it can be inverted without emerging from the water. The water was maintained at a temperature of 36-37°C as the immersion fluid. The test requires three suppositories and the procedure is applied to each of the suppositories [12], using disintegration tester (COPLEY type: NE4-COPD:UK·NG42JY).

3.5. Determination of melting point:

The determination of melting point provides precise information for excipient control. It was done according to the described method using (BUCHI Melting Point B=540) [7].

3.6. Suppository penetration test:

The temperature is adjusted to 37 °C that required for the test. The suppository is placed in the device and the penetration rod gently moved into place [7,12], using penetration tester (Erweka. PM3)

3.7. In vitro release of Levodropropizine from solid suppository bases:

The USP rotating paddle dissolution apparatus (COPLEY NEG-CIP-UK serial No:19695) was used for the release of Levodropropizine from solid suppository bases in vitro under following conditions: 30 min, in 250 mL phosphate buffer, 37°C, pH=7.2 and 50 rpm [13, 7, 14, 15]. Wire sinker was used to prevent floating on the surface of the dissolution medium [14]. Samples (5mL) were taken every 5 min from the release medium and replaced by fresh buffer. The samples were filtered through Millipore filter (pore size 0.45 μ m; Xiboshi, syringe filter, China) and analyzed spectrophotometrically at 240 nm against a blank puffer. Each release experiment was performed in triplicate. The validation process was done for the analytic method [16].

3.8. Kinetic analysis of the release data:

In order to describe the release model, the in vitro release data from solid suppositories were analyzed according to a zero-order kinetic model, a Higoshi model, first-order model, Hixon model, and Peppas model. The model that consistently produced the highest correlation among the suppository preparations was used for the assessment of drug release rates.

For Peppas model when $0.5 < n < 1$ means a non-Fickian dissolution model and $n = 0.45$ indicates Fickian diffusion (Higuchi Crowell model). In the case of a cylinder 0.45 (suppositories) instead of 0.5, and 0.89 instead of 1.0 [17].

3.9. Statistical analysis of the drug release profile:

All the results were expressed as mean values \pm standard deviation (SD). The difference between percentages (fractions) of Levodropropizine release after each 5 min from its various formulations (The chosen response for analysis) were statistically evaluated by using two ways ANOVA. All data analysis were performed using SPSS® 10.0 statistical software (SPSS Inc., Chicago, IL, USA). *P* value was significant at $p < 0.05$ for results interpretation.

RESULTS AND DISCUSSION

1. Physical properties of tested suppositories:

The weight variation study for all the suppositories were found to be within the acceptable range (<5%) [11]. Also, the drug content of each suppositories, from each formulation, was in the acceptable range (85-115)% [7]. The mechanical strength of all tested suppositories was over 1.8 kg showing optimum hardness for handling and transportation [7]. The melting points of all investigated suppositories with fat bases fell within 31.0 – 36.3°C, thus obeying pharmacopoeial requirements. It is established that surfactants added in the indicated concentrations lead to depression of the melting point of confectionary fat within 0.5 – 3°C depending on the nature of excipient[18]. The melting points of suppositories with water soluble bases were within 40-45.6°C, because of their high melting point suppositories are especially suited for application in tropical climates[19]. The softening time of all suppositories varied within 30 min depending on the particular types of components and was within the pharmacopoeial limits[7] expect F10; its soften time was 61.45 min that may be due to the poloxamer was gelled in water[20]. The disintegration time of all suppositories was within 30 min for fat bases, 60 min for hydrophilic bases and was within the pharmacopoeial limits [12]. Physical properties of suppositories are summarized in (Table 2)

Table 2: physical characterization of tested solid suppository formulations

Code	Weight variation (g)	Drug content(%)	Hardness(kg)	Melting point(°C)	Liquefaction time(min)	disintegration time(min)
F1	1.33±0.00889	100.67±2.08	3.66±0.11	45.46±0.4	8.4±0.5	21.66±1.527
F2	1.309±0.028	93.2±2.2	2.72±0.11	41±1	4.83±0.28	19.6±0.57
F3	1.305±0.0059	86.115±0.61	2.33±0.11	41.3±0.51	3.16±0.28	19.66±0.57
F4	1.069±0.004	98.93±2.6	5.33±0.11	35.63±0.55	7.03±0.52	10.4±0.52
F5	1.076±0.005	104.15±1.2	5.06±0.11	34.4±0.50	5.16±0.28	6.75±0.42
F6	1.098±0.003	105.21±1.3	3.53±0.11	32.53±0.5	4.5±0.5	3.47±0.56
F7	1.073±0.0042	100.53±2.2	4.86±0.11	35.36±0.47	5.41±0.11	10.56±0.404
F8	1.085±0.009	106.72±2.4	3.66±0.11	33.4±0.24	5.23±0.251	8.38±0.16
F9	1.091±0.007	99.89±0.76	3.53±0.11	31.4±0.4	4.06±0.115	7.1±0.173
F10	0.98±0.017	102.87±1.31	3.06±0.11	45.53±0.503	61.45±1.7	42.66±0.404
F11	1.04±0.007	103.2±2.3	2.73±0.11	33.03±0.152	22.38±0.53	18.33±0.577
F12	1.13±0.0072	102.44±1.68	2.13±0.11	32.53±0.503	8.56±0.404	14.33±0.57

2. In vitro release rate of Levodropropizine from hydrophilic bases:

The dissolution profiles of Levodropropizine from suppositories formed using different compositions of PEG, F1, F2, and F3 are shown in Figure 1.

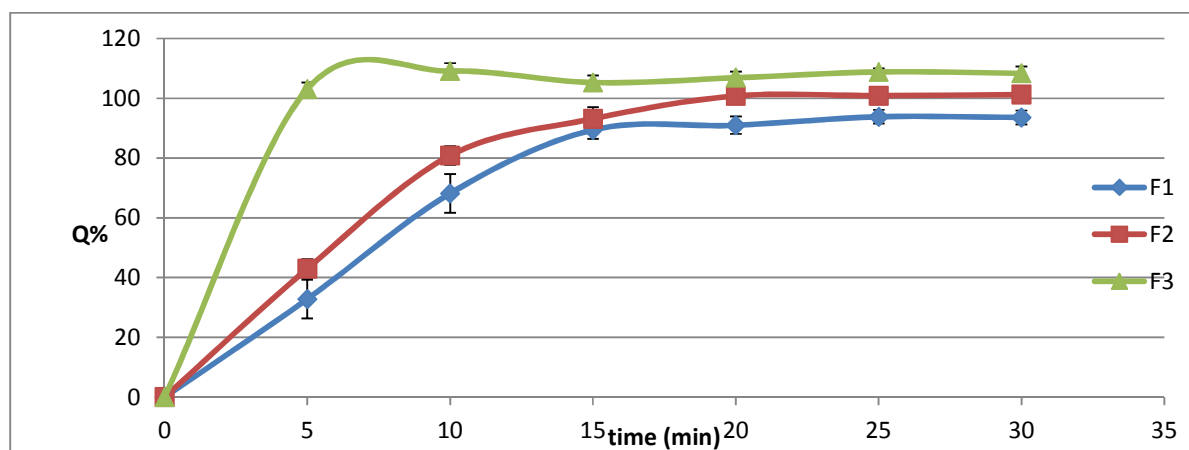


Figure 1: Release of levodropropizine from various Hydrophilic PEG bases

Statistical analysis revealed a significant difference ($P < 0.05$) between F1, F2 and F3, within the Levodropropizine release rate study.

The release rate of Levodropipizine from the suppositories was relatively high, it reached almost the total amount of drug at 20 min for F1/F2 and at 5 min for F3. The dissolution of slightly soluble substances, Levodropipizine[10], can easily be the slowest step in the absorptive process, so when the dissolution of drug is increased the absorption will be improved [22]. PEGs improve dissolution of drugs because of the absorbing properties of PEG[21, 22], which result in the formation of a hydrophilic matrix with following solubility enhancing effects. This result was in agreement with the kinetic analysis of the results, which exposes a Hixson-Crowell model for all tested PEG formula, where the dissolution occurs in planes that are dispersed parallel to the drug surface, if the dosage form sizes reduce regularly by time[17](Table 3). It is known that, as the molecular weights of PEG increase, their water solubility and hygroscopicity decrease[23]. According to the extent of drug release, the results were as follow: F3 > F2> F1 (Figure1).

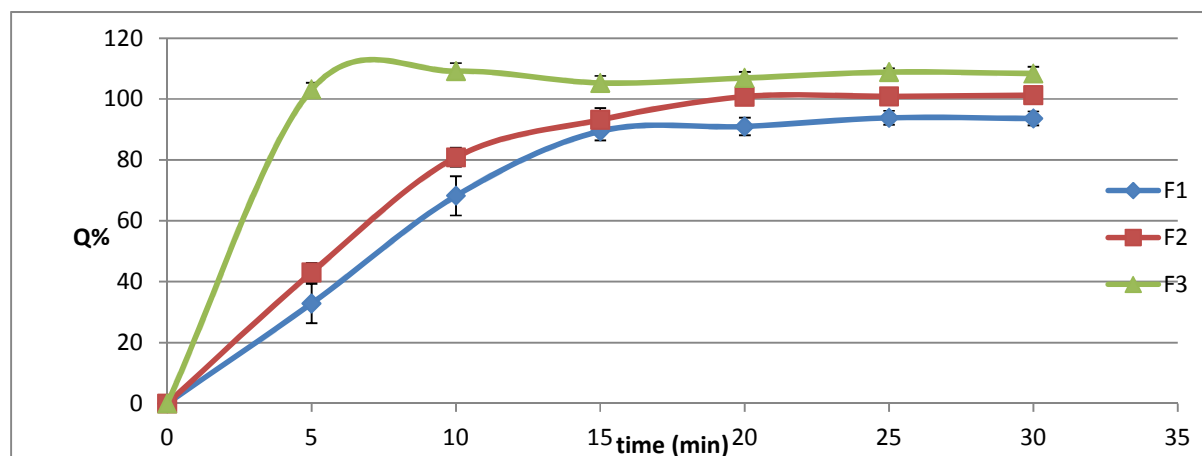


Figure 1: Release of levodropipizine from various Hydrophilic PEG bases

Drug partitioning is a function of the nature of base and the affinity of the drug towards the base. It is to be noticed that the base with the highest hydrophilicity, F3, is gone by the highest drug release profile (100% extent release at 5min). F3 has a high ratio of PG, which is most likely to have more hydrophilic character and it will work as co-solvent and Plasticizers[24]. This was reflected in the drug release, but propylene glycol affected the hardness of suppositories and decreased the melting point which was the lowest in F3, (Table2).

Table 2:physical characterization of tested solid suppository formulations

Code	Weight variation (g)	Drug content(%)	Hardness(kg)	Melting point(°C)	Liquefaction time(min)	disintegration time(min)
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F4	1.069±0.004	98.93±2.6	5.33±0.11	35.63±0.55	7.03±0.52	10.4±0.52
F5	1.076±0.005	104.15±1.2	5.06±0.11	34.4±0.50	5.16±0.28	6.75±0.42
F6	1.098±0.003	105.21±1.3	3.53±0.11	32.53±0.5	4.5±0.5	3.47±0.56
F7	1.073±0.0042	100.53±2.2	4.86±0.11	35.36±0.47	5.41±0.11	10.56±0.404
F8	1.085±0.009	106.72±2.4	3.66±0.11	33.4±0.24	5.23±0.251	8.38±0.16
F9	1.091±0.007	99.89±0.76	3.53±0.11	31.4±0.4	4.06±0.115	7.1±0.173
F10	0.98±0.017	102.87±1.31	3.06±0.11	45.53±0.503	61.45±1.7	42.66±0.404
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F12	1.13±0.0072	102.44±1.68	2.13±0.11	32.53±0.503	8.56±0.404	14.33±0.57

Statistical analysis revealed a significant difference ($P<0.05$) between F10 and F11, F10 and F12, where there was no significant difference ($P<0.05$) between F11 and F12 within the Levodropipizine release rate analysis.

For Poloxamer based suppositories (Figure 2) releasing from F10 which contains poloxamer 188 100% had a lower dissolution rate of Levodropipizine than PEG based suppositories, that because PEG was soluble in the dissolution medium, while poloxamer was gelled, and the formed gel neither absorbed water nor was it hydrophilic [23] due to the hindrance of the hydrophobic polyoxypropylene part of the molecule by the hydrophilic polyoxyethylene part of

the molecule [25]. While the dissolution rate of Levodropropizine from F11/F12, which contained PG, was high because propylene glycol affected the melting point of poloxamer mixtures[26], and due to the hygroscopic properties of propylene glycol, which caused increased water absorption and the formation of a hydrophilic polymer matrix. The mechanism of drug release was found to be Higoshi-model that means the mechanism of release of Levodropropizine is diffusion through the hydrophilic matrix of poloxamer 188/propylene glycol bases. Data from Peppas model revealed n values between 0.45 and 0.89 for F10 that mean the mechanism of drug release is (non-Fickian) [17], where the release is controlled by a combination of diffusion and polymer relaxation, (Table 3).

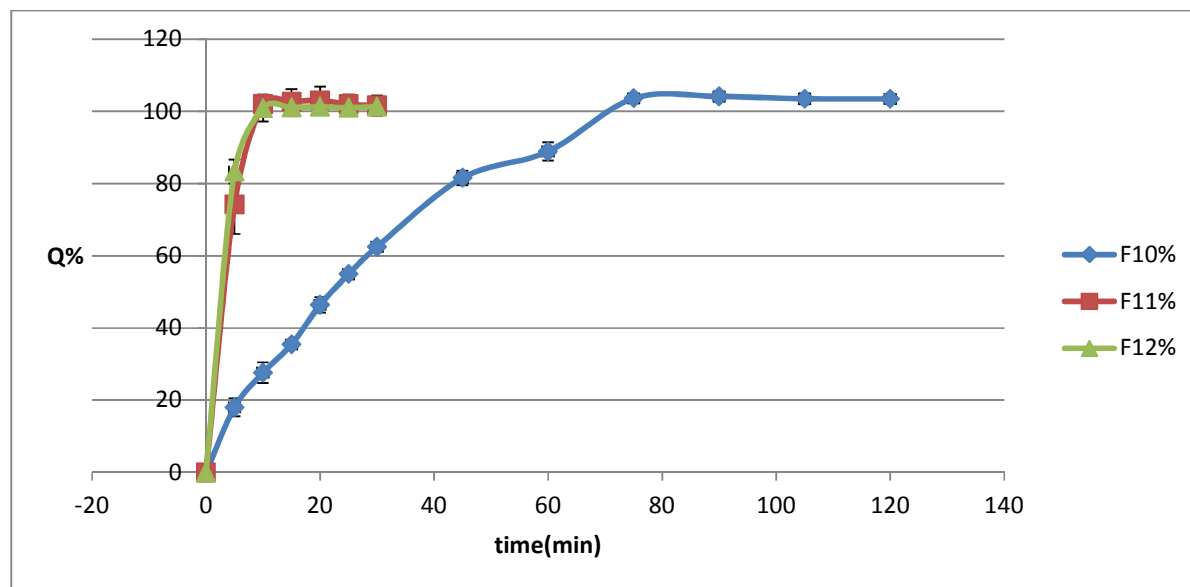


Figure 2: Release of levodropropizine from various Hydrophilic Poloxamer bases

The Poloxamer suppositories would be more acceptable to patients because of; low toxicity, less skin irritation, good drug release characteristics, compatibility with other chemicals and keeping the drug in the lower part of the rectum compared to conventional suppositories[27]. The problem associated with PEG suppositories is migration of drugs, that may undergo first-pass metabolism, up to the colon and irritation of rectum mucus[28].

The influence of PEG/Poloxamer on the dissolution of the Levodropropizine can be explained by the formation of regions with high concentration of dissolved polymer at the surface of drug crystals. In this regions; the drug can solubilize and subsequently diffuse and dilute in the bulk of the solution. Formulation of solid dispersions could theoretically further improve the dissolution compared with physical mixtures by reducing the drug particle size, formation of drug/polymer solid dispersion, transformation of the drug to the faster dissolving amorphous state and by more intimate contact between the polymer and the drug [20].

Table 3: In-vitro release kinetic parameters of levodropropizine from the suppositories

Formula	Zero order(r2)	First order(r2)	Higoshi(r2)	Hixon(r2)	Papas(n)	Papas(r2)
F1	0.9141	0.7208	0.956	0.9624		
F2	0.8659	0.6869	0.9326	0.9751		
F3	0.9019	0.6958	0.9675	0.9833		
F4	0.9718	0.7705	0.9838	0.9176		
F5						
F6	0.9838	0.858	0.8626	0.8286		
F7	0.9692	0.9191	0.8019	0.725		
F8						0.9844
F9	0.924	0.728	0.9218	0.9318	1.8184	
F10	0.9499	0.6113	0.9787	0.9345		
F11	0.9835	0.8482	0.9888	0.9345		0.9929
F12	0.949	0.8227	0.9999	0.9345	0.6895	

3. Release of Levodropropizine from fatty bases:

Release rate of Levodropropizine from two different types of semi synthetic fatty bases was studied (Figure 3, 4).

Statistical analysis revealed a significant difference ($P < 0.05$) between (F4, F5, F6), (F7, F8, F9) and (F4, F7) within the Levodropropizine release rate study.

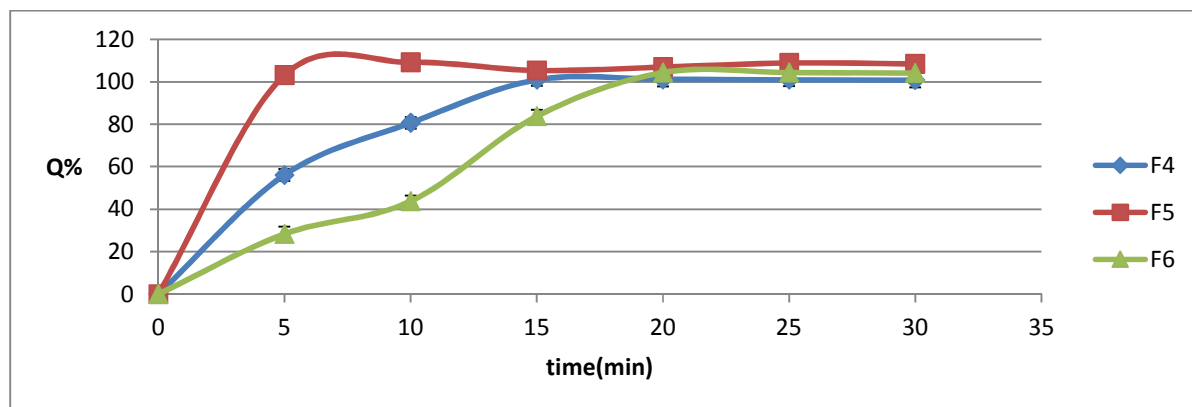


Figure 3: Release of levodropropizine from various Hydrophilic Witepsol H15 bases

A complete melting of a suppository in the dissolution medium is certainly required for the drug to be completely released. The results according to the percent extent drug release was as follows: Witepsol H15 > Novata BCF. Semi-synthetic suppository bases are mixtures of fatty acids and esters with certain amounts of glycerides. The hydroxyl values reported the free hydroxyl functional groups that are available for interaction and reflected the potential for a base to adsorb water [29,22].

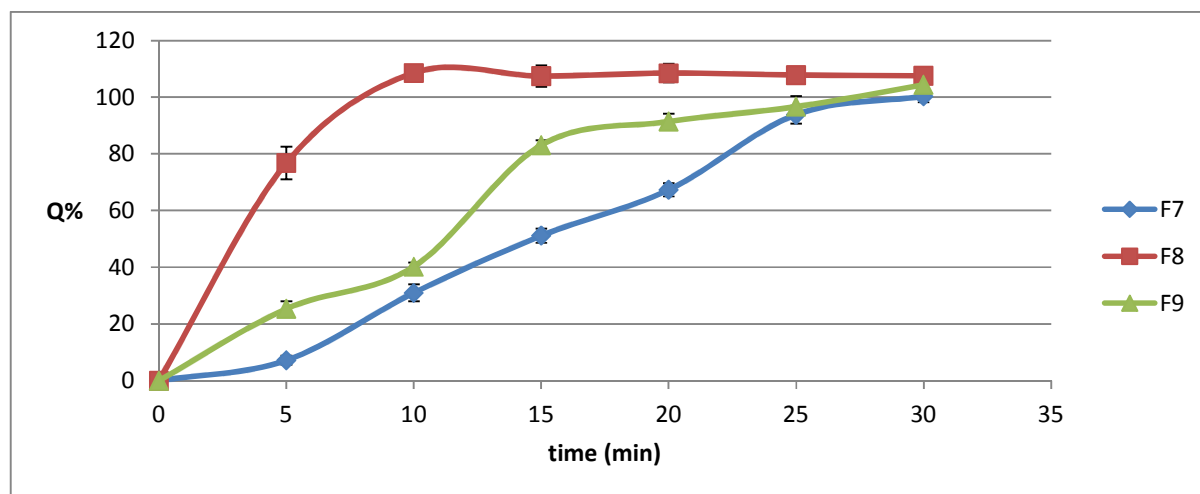


Figure 4: Release of levodropropizine from various Hydrophilic Novata BCF bases

The presence of a high hydroxyl value in fatty bases could form a water-in-oil emulsion, which will generally result in a very slow transfer of drug molecules from the inner aqueous phase, i.e. retarded drug release [30,22]. Therefore, drug release from Suppositories of Novata BCF, which has a high hydroxyl value of 20-30[31], was lower than those from suppositories of Witepsol H15 (hydroxyl value 5-15) [32]. The mechanism of releasing the drug from Witepsol H15(F4) was found to be a diffusion Higuchi model, which means the diffusion is the mechanism of drug releasing from the suppositories. Mechanism of drug releasing from Novata BCF(F7) was zero order, the pharmaceutical dosage forms following this profile release the same amount of drug by unit of time, (Table 3), and it is the ideal method of drug release in order to achieve a pharmacological prolonged action [17].

Effect of Tween 80 that is put with Witepsol H15 in F5/F6 and Novata BCF was studied on Levodropropizine release. All kinds of surfactants seem to do the promoting work on releasing drugs from suppositories [22]. Tween 80 is an example of a hydrophilic, non-ionic surfactant (hydrophilic-lipophilic balance (HLB) = 15[33]). The incorporation of Tween 80 affected the rate of medicament release depending on the nature and concentration of surfactant[34]. Drug release from Witepsol H15 and Novata BCF was completed in F5/F8 at 5 min, when Tween 80 percentage was 5% in the suppositories. Drug release is the result of melting the base, migration of drug particles to the interface between the melted excipients and the dissolution medium, and of the particles passage through this interface to be released in a molecular form[35]. Therefore, drug was incorporated in the base in the form of an aqueous solution instead of the powder form using Tween 80 for emulsification that lowered the interfacial tension, and increased dispersibility of the suppository base with the dissolution fluid [34]. Results showed that Tween 80 had maximum effect on the rate enhancement of drug release (100% of the drug was released in 5 min). The mechanisms could be as a result of their moistening effects which increase the surface area of the suppository mass, and also shortening disintegration times of lipophilic suppositories, which is caused by changing their lipophilic characteristics to a lipohydrophilic nature[36].

However, further addition of Tween 80 up to a concentration of 10% in F6/F9 increased the release rate of the drug, but it took more time to release drug than suppositories contained Tween 80 at 5% concentration. At higher concentrations, the surfactant might have exceeded its critical micellar concentration (CMC), and thus retarded drug release, as a result of micellar entrapment of the drug[37]. The mechanism of drug releasing from Witepsol, which contained Tween 80 at 10% was found to be a zero order. Data from Peppas model revealed a n values above 0.89 for F7, which means zero order for the mechanism of drug release [17]. Mechanism of drug releasing from Novata BCF, which contained Tween 80 at 10% was Hixson-Crowell model for, where the dissolution occurs in planes that are dispersed parallel to the drug surface, if the dosage form sizes reduce regularly by time. (Table 3)

CONCLUSION

In conclusion, levodropropizine suppositories were prepared using fat and hydrophilic bases. Physicochemical properties of suppositories were studied. Incorporation of non-ionic surfactants to fat bases at low concentrations improved drug release. A very fast release of the drug was achieved by incorporating the drug as an aqueous solution in Witepsol H15. Suppositories composed of Poloxamer 188 with PG have shown remarkable immediate release of the drug. The formula that contained 30% PG could be regarded as a promising mucoadhesive release formulation suitable for further investigation.

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