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Emulsions and rectal formulations containing myrrh essential oil for better patient compliance

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ABSTRACT: Myrrh has long been used for its circulatory, disinfectant, analgesic, antirheumatic, antidiabetic, and schistosomicidal properties. Myrrh essential oil (MEO) was extracted from the oleo-gum resin of *Commiphora molmol* and formulated into emulsions and suppositories to mask/avoid its bitter taste. Three oil-in-water emulsions (E1-E3) were formulated and taste was evaluated by 10 volunteers. Particle size distribution was measured and correlated with excipients and the method of preparation. Physical and chemical stability testing was carried out for the optimum formulation (E2). Seven suppository formulations were investigated (F1-F7). Suppocire AML (F1) and Suppocire CM (F2) were chosen as fatty bases, and polyethylene glycol (PEG) 1500 (F3), PEG 4000 (F4), and a PEG blend (50% PEG 6000 + 30% PEG 1500 + 20% PEG 400) (F5) were chosen as water-soluble bases. A blend of PEG 1500 and Suppocire CM was also used (F7). Camphor (5%) was added to PEG 1500 (F6). Disintegration time, release rate, DSC, fracture points, and weight uniformity were evaluated. The overall average bitterness for formulations E1, E2, and E3 was 6.44, 4.15, and 3.45, respectively. Suppositories containing Suppocire AML had the fastest disintegration time (1.5 min) with dissolution efficiency (DE) of 56.8%. F3 containing PEG 1500 had a fast disintegration time of 2.5 min and maximum DE of 93.5%. The PEG blend had satisfactory release: (DE = 90.9%). A mixed fatty and water-soluble base (F7) had a disintegration time of 5 min and low DE (33.4%). A stable MEO emulsion with acceptable taste was formulated to improve patient acceptance and compliance. F3 suppositories yielded satisfactory results, while formulations containing fat-soluble bases exhibited poor release.

Keywords: Myrrh essential oil, emulsions, taste masking, suppositories, release, stability

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1. Introduction

Myrrh (Arabian or Somali Myrrh) is an oleo-gum resin, obtained from the stem of various species of *Commiphora*, Family Burseraceae, growing in north-east Africa and Arabia (*1*). The chief source is *Commiphora molmol*. The volatile oil obtained from *C. molmol* is thick and pale yellow (*2*). The constituents of the essential oil include cadinene, elemol, eugenol, cuminaldehyde, furanosesquiterpenes, furandiene, furanodienone, curzerenone, lindestrene, and furanoeudesma-1,3-diene (*1*,*3*,*4*). The oil has been used to treat sore throats, canker sores and gingivitis, acne, boils, and arthritis (*5*).

An extract of myrrh (gum) effectively decreased the absolute increment of blood glucose above the fasting concentration at all times in an oral glucose tolerance test with both normal and diabetic rats (*6*). Myrrh is also used in cosmetic preparations to treat the hair and scalp (*7*). In addition, myrrh has anti-inflammatory activity, antipyretic activity (*8*), anti-ulcerogenic activity, and offers protection against mucosal damage caused by indomethacin (*9*). Myrrh is not recommended during pregnancy as it is a uterine stimulant and excessive oral doses (2-4 g) may lead to diarrhea, heart rate changes, and kidney irritation. Myrrh has been found to have cytotoxic and antitumor activity equivalent to that of the standard cytotoxic drug cyclophosphamide (*10*).

Myrrh could be used therapeutically to chelate toxic metals, thus potentially reducing their toxicity and tissue damage (*11*). The sesquiterpene fractions of myrrh have antibacterial and antifungal activity against standard pathogenic strains of *Escherichia coli, Staphylococcus aureus*, and *Pseudomonas aeruginosa* (*12*).

In the last few years, a myrrh extract purified using methyl alcohol has been formulated and marketed as soft gelatin capsules (MIRAZID®) to treat *Schistosoma mansoni* and *Schistosoma haematobium* (*13*). Recently, the efficacy of this new anti-schistosomiasis drug was questioned by several research articles describing the administration of MIRAZID® as having a very limited antischistosomal effect (*14*,*15*). More recently, Nomicos reported on the numerous uses of myrrh from antiquity to the present (*16*).

Emulsions can be designed for oral administration. An oil-in-water (O/W) emulsion is a convenient means of orally administering water-insoluble liquids, especially when the dispersed phase has an unpleasant taste, *e.g.* a cod liver oil emulsion (*17*). More significant in contemporary pharmacy is the observation that some oil-soluble compounds, such as some vitamins, are absorbed more completely when emulsified than when administered as an oily solution.

Rectal delivery is an alternative to the oral route because it can decrease gastrointestinal side effects, avoid undesirable effects of meals on drug absorption, and is also useful when vomiting is present – a situation particularly relevant to young children. However, the choice of a suppository base is paramount since drug release from a suppository base is often the rate-determining step in the absorption process and, consequently, the onset of drug action (*18*).

In this study, various O/W emulsion and suppository formulations were prepared to mask/avoid the unpleasant taste of myrrh essential oil (MEO) serving as the active ingredient. Two types of suppository bases, fatty bases and water-soluble bases, were used in addition to a blend of a water-soluble and a fatty base.

2. Materials and Methods

2.1. *Materials*

Aspartame, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), and EDTA were from Jebsen & Jessen, Hamburg, Germany. Anise oil and peppermint oil were supplied by Burnet, Italy. Cremophore RH40 and polyethylene glycols (PEGs) were procured from BASF, Schwarzheide, Germany. Myrrh (oleogum resin; Somali origin) was supplied by Emiga, Gardanne, France. Xanthan gum was from Red Carnation Gums Ltd., Basildon, UK. Methyl and propyl paraben were from Suntin MediPharma Co. Ltd., Shenzhen, China. Petroleum ether 40-60 and camphor were from El-Nasr Pharmaceuticals, Alexandria, Egypt. Propylene glycol was from Lyondell, France. Citric acid was from Jungunzlauer, Basel, Switzerland. Suppocire CM and Suppocire AML were supplied by Gattefosse, Lyon, France.

2.2. *Preparation of MEO*

The particle size of oleogum resin was reduced in the following two steps: trituration using a mortar and pestle followed by further refining using a small scale electric grinder. Subsequently, percolation was performed using 1 L petroleum ether 40-60 as a solvent for each kg of oleogum resin (*19*). The solvent was left overnight before collection and the procedure was repeated 3 times in succession in an attempt to ensure the complete extraction of the late-eluting fractions of the oil. The three crops of the percolate were added together and the oil was separated from petroleum ether using a rotary evaporator at 50°C. The resulting oil was a pale yellow viscous liquid.

2.3. *Preparation of MEO Emulsions*

MEO emulsions were prepared according to the formulations shown in Table 1. The emulsifier Cremophore RH40 was subjected to slight warming on a water bath before the oil mixture (the flavoring agents anise, peppermint oil, and myrrh) was added, and the result was sonicated for a few minutes. Water containing citric acid was warmed until its temperature slightly exceeded the cremophore/oil mixture before it was added to the oily phase, and the result was homogenized at a fixed speed of 6,500 rpm (Ultraturrax T25, IKA Labortechnik, Staufen, Germany). Preliminary trials using various homogenizing speeds revealed this to be the optimum speed. Xanthan gum (viscosity imparting agent), which was left in a closed container overnight at room temperature for optimum hydration, was added to the formed emulsion along with the prepared simple syrup. BHA (antioxidant) and methyl and propyl parabens (preservatives) were incorporated after dissolution in the ethanol/propylene glycol mixture. Finally, EDTA (chelating agent) was added to the water in order to bring the emulsion to its final volume and produce a creamy white liquid product.

2.4. *Physicochemical evaluation of emulsions*

2.4.1. *Taste*

A study was carried out to evaluate the taste of three formulations using a taste panel (ten volunteers). The test was performed as previously reported in the literature (*20*) with a modification: the taste panel was asked to report

Table 1. Percent (w/w) of the individual ingredients used for preparation of the proposed emulsion formulations

Components	Formulations		
	E1	E2	E3
Cremophore RH40	2.00	2.00	2.00
Myrrh Essential oil	3.60	3.60	3.60
Citric acid	0.01	0.01	0.01
Aspartame	0.40	0.40	0.40
Xanthan gum	0.15	0.15	0.15
Sucrose	40.00	40.00	40.00
Ethanol	5.00	5.00	5.00
Propylene glycol	2.00	2.00	2.00
Methyl paraben	0.06	0.06	0.06
Propyl paraben	0.06	0.06	0.06
BHA	0.02	0.02	0.02
EDTA	0.10	0.10	0.10
Anise oil	–	0.10	0.10
Peppermint oil	–	0.10	0.10
Glycerol	–	–	30.00
Water	to 100	to 100	to 100

initial bitterness (1st round) and sustained bitterness (2nd round) instead of a single round of testing. The average bitterness was calculated from these 2 rounds and taste was rated on a scale where 1 was acceptable and 10 was completely unacceptable. The taste panel was allowed to rinse their mouths out with water and wait 10 min before tasting the next formulation. The three formulations were tested in random order.

2.4.2. *Particle size determination*

A laser particle size analyzer (Model 1064; CILAS, Orleans, France) was used to determine the size of oil droplets (*21*) in the range of 0.04-500 μm. Particle size distribution was correlated with the effect of excipients and method used for emulsion preparation.

2.4.3. *Physical stability*

A temperature cycling method was used in which the emulsion was stored at an elevated temperature (45°C) for 48 h and then refrigerated (4°C) for 48 h (*22*). The effect of centrifugal force on the stability of the prepared emulsions was evaluated at the following two speed levels (*16*): *i*) high speed, 4,000 rpm for 2 min and *ii*) low speed, 2,000 rpm for 6 min.

2.4.4. *Chemical stability*

The E2 emulsion was evaluated in terms of the stability of MEO content over three months at 25°C and 4°C. A colorimetric method was used to determine MEO in the emulsion (*19*). The calibration curve was constructed using a stock standard solution of MEO (5 mg/mL) in methanol. Aliquots of the stock standard solution ranging from 400-2,000 μL were transferred to 2 mL screw-capped test tubes. To each tube, 5 mL of 1% (w/v) vanillin solution and 1 mL of methanol were successively added. The tubes were capped and heated in a water bath at 60°C for 60 min, allowed to cool for 30 min, and then the contents were transferred to 50 mL volumetric flasks and brought to final volume with methanol. The absorbance of the developed violet color was measured against a reagent blank at 518 nm (Helios alpha UV-Visible spectrophotometer, Thermo Spectronic, Cambridge, UK). A 7 mL volume of the well mixed oral emulsion, equivalent to 252 mg of MEO, was transferred to a 50 mL-volumetric flask, dissolved in methanol, and then brought to final volume with methanol. Aliquots of this solution (1,000 μL) were treated using the above described procedure prior to spectrophotometric analysis at 518 nm.

A placebo formulation was tested using the same procedure of determining MEO to ensure no interference from any of the excipients used. A characteristic violet color should not develop in the absence of the active component.

2.5. *Suppository formulations*

Seven different suppository formulations (F1-F7) were prepared using the fusion method and employing different bases (Table 2). Suppocire CM and AML were chosen as fatty bases while PEG 1500, PEG 4000, and a PEG blend (50% PEG 6000 + 30% PEG 1500 + 20% PEG 400) were used as water-soluble suppository bases. A blend consisting of 70% PEG 1500 and 30% Suppocire CM was also investigated. Camphor (5%) was added to PEG 1500-based suppositories (F6). BHT was included in all formulation (0.4%) as an antioxidant. MEO was added to the melted base (180 mg MEO/supp) and the resulting mixture was then poured into a metal mold and allowed to cool. The prepared suppositories were stored at 4°C until use.

2.6. *Physiochemical evaluation*

The displacement values of MEO in each suppository base are shown in Table 2. Uniformity of weight was evaluated using 20 suppositories of each formulation and the average and standard deviation were calculated.

Differential scanning calorimetry (DSC) thermograms were obtained (DSC 6, Perkin-Elmer, Waltham, MA, USA) for the pure base and final formulation. Samples (20 mg) were heated in aluminum pans at a rate of 2 °C/min over a temperature range of 25 to 125°C. The values for the transitions were derived from the computed extrapolated peak maximum and onset and end of melting, and the enthalpy values (ΔH) were calculated from the area under the melting peak.

Disintegration was tested using a tablet disintegration tester (QC-21; Hanson Research, Chatsworth, CA, USA) and suppositories stored for 24 h at room temperature. Water (37 ± 0.5°C) was used as the immersion fluid and the time required for each suppository to completely melt or dissolve was measured.

Fragility of suppositories was determined using a fracture point apparatus (Model SBT; Erweka GmbH, Heusenstamm, Germany) equipped with a double-walled chamber to maintain the desired temperature at 25°C. Each suppository was subjected to an initial load of 0.6 kg. After 1 min, a metallic disc weighing 0.2 kg was

Table 2. Displacement values of MEO in each suppository base used

Formulations	Suppository base (each containing 180 mg MEO)	D.V.*
F1	Suppocire AML	1.22
F2	Suppocire CM	0.94
F3	PEG 1500	1.00
F4	PEG 4000	0.92
F5	PEG mixture (50% PEG 6000, 30% PEG 1500, 20% PEG 400)	1.05
F6	PEG 1500 containing 5% camphor	1.00
F7	70% PEG 1500 + 30% Suppocire CM	1.30

* Displacement value of the suppository base.

added and the process continued until the suppository collapsed. If breaking occurred within the first 20 sec after application of the additional disc, only the sum of the previous weights was considered. If it collapsed in 20-40 sec, only half the value of the additional weight was added to the sum. If breaking occurred after 40 sec, the additional weight was fully considered.

An *in vitro* drug release test was carried out using Dissolution Tester USP-25, apparatus 1 (Model TDT-O6N; Electrolab, Mumbai, India). The medium consisted of 450 mL phosphate buffer, pH 7.4, with 3% sodium lauryl sulphate maintained at 37 ± 0.5°C and the paddles were rotated at 100 rpm. Aliquots were withdrawn at 5, 10, 15, 20, 30, 45, and 60 min. Samples were then suitably diluted and the amount of MEO was determined by reaction with freshly prepared vanillin sulfuric acid followed by spectrophotometric measurement at 518 nm using an appropriate blank. Details of this method have been previously described (*19*). The data presented are the average of three determinations.

3. Results and Discussion

3.1. *Emulsions*

3.1.1. *Taste*

To evaluate the improved taste and lack of bitterness of formulations, the taste of the prepared emulsions was evaluated. Table 3 shows the results of a taste evaluation by ten volunteers. The overall average bitterness for formulations E1, E2, and E3 was 6.5 ± 0.8, 4.2 ± 1.3, and 3.5 ± 0.6, respectively. The simple use of natural and synthetic sweetening agents such as sucrose and aspartame (E1) was not sufficient to make a product containing a drug with a particularly unpleasant taste, such as myrrh, more palatable. The use of an anise/peppermint oil mixture in E2 increased the formulation's acceptance by volunteers. Anise and peppermint oils are common ingredients in pediatric formulations. This may be particularly useful in improving patient compliance. Moreover, anise and peppermint have proven to be particularly useful in masking a bitter taste in comparison to other flavors (*23*). The use of glycerol in E3 further increased acceptance by volunteers. This could be due to the additional sweetening effect of glycerol. However, formulation E3 containing glycerol had less physical stability than E2 that lacked glycerol, as evidenced by the greater particle size distribution of E3 in comparison to E2 (Table 4).

Table 3. Taste evaluation of the prepared emulsions by a panel of ten volunteers

Evaluation	Formulations		
	E1	E2	E3
1st round	4.8 ± 1.4	3.6 ± 1.6	2.7 ± 1.1
2nd round	8.1 ± 0.5	4.7 ± 2.4	4.2 ± 1.4
Average	6.5 ± 0.8	4.2 ± 1.3	3.5 ± 0.6

Data are shown as means ± S.D. (n = 10).

3.1.2. *Particle size analysis*

The particle size distribution of the prepared emulsions was evaluated in an attempt to examine the effect of emulsion composition on globule size since this may affect emulsion stability and appearance. Aliquots from each emulsion were appropriately diluted by the aqueous phase to a droplet concentration of approximately 0.0005% to avoid the effects of multiple scattering (*21*). The results of particle size analysis are summarized in Table 4. Incorporation of glycerol in E3 increased the particle size dramatically in comparison to E2.

With a formulation containing cremophore/anise/peppermint and MEO and no other excipients, none of the oil droplets exceeded 100 μm (the maximum diameter for oil droplets was 71 μm) and the diameter at 50% was 19.9 μm (Table 4).

The homogenization used to formulate emulsions yielded more satisfactory results than did the direct use of a magnetic stirrer. Homogenization produced particles with a diameter of 1.23 μm at 50% cumulative value and a maximum diameter of 140 μm compared to a diameter of 7.12 μm at 50% cumulative value and a maximum diameter of 240 μm when a magnetic stirrer was used (Table 4). Increasing the speed of homogenization above 6,500 rpm failed to improve the particle size distribution (Table 4). The adverse effect of increasing the homogenization speed on the droplet size distribution could be attributed to the partial breakdown of the structure formed by the emulsion stabilizer

Table 4. Effect of emulsion composition and stirring rate on particle size distribution

Formulation	Diameter at 10% (μm)*	Diameter at 50% (μm)*	Diameter at 90% (μm)*	Mean diameter (μm)
E2, 6,500 rpm	0.09	1.23	84.9	24.3
E2, 9,500 rpm	0.92	69.8	130	64.7
E2, 13,500 rpm	1.00	70.9	129	65.3
E2, magnetic stirrer	0.22	7.12	117	40.7
E2, Xanthan gum only	2.65	270	456	245
E3, 6,500 rpm	0.10	34.9	369	93.9
Emulsifier and oily ingredients	7.51	19.9	36.9	21.3

* Particle size corresponding to cumulative frequency distribution data.

xanthan gum (*24*). This structure is thought to be responsible for arresting oil droplets in place, preventing their adherence, coalescence, and hence growth in size.

3.1.3. *Physical stability*

The stability of the prepared emulsions (F1, F2, and F3) was determined by exposure to highly elevated and reduced temperatures in cycles. An elevated temperature (45°C) and a refrigeration temperature (4°C) were used for evaluation.

No changes were observed for up to 5 cycles of the elevated and refrigeration temperatures (data not shown). A centrifugation test was performed to examine the physical stability of the formulation; separation of a layer was deemed to indicate a product with a poor design and poor physical stability. No signs of creaming were observed after centrifugation at high (4,000 rpm) or low (2,000 rpm) speeds of centrifugation (data not shown). These results could be useful indicators of the stability of future formulations.

3.1.4. *Chemical stability*

Liquid dosage forms are known to be far less stable than solid or semisolid products. Therefore, the chemical stability of the emulsion of choice (Formulation E2) was monitored by analysis of its MEO content at the time of preparation (baseline) and 1, 2, and 3 months after emulsion preparation. The results of chemical analysis are shown in Table 5. The results clearly show that the emulsion maintained its oil quality over the period of examination when stored both on the shelf and in the refrigerator. However, UV spectrophotometric methods are not suitable for indicating chemical stability. Thus, the test used in this study only serves as a preliminary indication of the produced formulation's chemical stability. These results along with the results of physical stability indicate the suitability of the composition and method of its preparation to produce emulsions with acceptable properties.

Table 5. Percent of remaining MEO in formulation E2 during storage at various temperatures

Storage period	Remaining MEO in E2 (%)	
	25°C	4°C
Baseline	100.0	100.0
1 month	100.0	97.6
2 month	98.3	99.0
3 month	98.0	98.3

3.2. *Suppositories*

3.2.1. *Uniformity of weight*

All of the prepared suppositories had acceptable results with regard to the uniformity of weight described in BP 2004 (*25*) (data not shown). No more than two of the individual weights deviated from the average weight by more than 5% and none deviated by twice that percentage; the standard deviations of the prepared formulations ranged from ± 0.01 to ± 0.06. The BP does not require uniformity of content for suppositories containing more than 2 mg or 2% of the total mass; drug content in the investigated suppositories was 3.6%.

3.2.2. *Differential scanning calorimetry (DSC)*

The data derived from DSC thermograms of the prepared suppositories are summarized in Table 6. A decrease in the melting points of the suppositories was observed with all formulations in comparison to the respective base. This could be explained by the liquid nature of MEO. Mixing camphor with PEG 1500 led to a slight reduction in the melting point of the base; melting points were 49.3 and 50.8°C, respectively. On the other hand, inclusion of the oil (MEO) in camphor suppositories containing PEG 1500 led to an increase in the melting point from 49.3 to 59.3°C. This increase may be explained by the interaction between PEG and some of the components of MEO, which resulted in higher molecular weight compounds. This may be a consequence of ether formation by the free –OH groups of PEG and free –OH groups of elemol and eugenol present in MEO and the formation of high molecular weight compounds, which are expected to have higher melting points. Similar interactions involving transesterification of PEG with aspirin (*26*) and pancreatin (*27*) have previously been reported in the literature.

Table 6. Parameters obtained from DSC thermograms of suppository bases before (A) and after (B) the incorporation of MEO

Parameters	F1		F2		F3		F4		F5		F6		F7	
	A	B	A	B	A	B	A	B	A	B	A	B	A	B
Peak (°C)	38.9	35.7	40.6	37.6	50.8	46.7	63.4	60.6	58.4	55.7	49.3	59.3	49.5	35.4
Peak Height (MW)	12.2	7.5	14.9	9.8	26.6	14.8	32.5	20.5	13.1	8.8	22.1	16.4	21.4	7.0
Area (MJ)	5,894	3,797	4,934	5,048	5,954	5,081	6,442	6,284	5,964	5,226	8,682	4,502	5,699.5	4,477
Delta H (J/G)	294.7	189.8	246.7	252.4	297.7	254.0	322.1	314.2	298.2	261.3	434.1	225.1	284.9	223.9
End (°C)	40.8	37.8	42.6	39.6	53.0	48.7	66.4	62.5	60.5	57.5	51.5	61.1	51.6	37.8
Onset (°C)	35.7	25.1	38.1	32.3	47.1	37.9	60.5	58.2	54.8	50.0	46.2	56.2	46.9	28.0

The lowest melting points were observed with Suppocire fatty bases, *i.e*. 35.7 and 37.6°C for Suppocire AML (F1) and Suppocire CM (F2), respectively. The melting point of a Suppocire AML-based suppository (F1) was sufficient to allow melting at body temperature shortly after insertion. Suppositories prepared using PEG bases had melting points ranging from 46.7 to 60.6°C (F3 to F6). A mixed base suppository formulation (F7) had a lower melting point of 35.4°C.

3.2.3. *Disintegration time*

According to BP 2004 (*25*), suppositories of water-soluble bases are supposed to dissolve within 60 min and those of fatty bases should soften and melt in no more than 30 min. The results of the disintegration experiments are shown in Table 7. Results revealed that fatty bases (Suppocire AML and Suppocire CM) (F1 and F2, respectively) typically had faster disintegration times than water-soluble bases. Of water-soluble bases, PEG 1500/camphor-based suppositories (F6) had the fastest disintegration time while PEG 4000 (F4) had the slowest disintegration time, *i.e.* 2 and 15 min for F6 and F4, respectively.

3.2.4. *In vitro drug release*

The percentage of drug released after 30 min was chosen for comparison of the *in vitro* drug release from various suppository bases (Figure 1). Moreover, the percentage dissolution efficiency (DE%) values obtained from the dissolution profiles of the drug from different suppository bases have been calculated using the following equation:

DE% = (Area under dissolution curve to a certain time)/(Area of the rectangle of 100% dissolution in the same time) × 100

The areas under the dissolution profiles (Figure 1) were calculated using the trapezoidal principle and the respective dissolution efficiencies are shown in Table 7.

The fastest release was observed with suppositories based only on PEG 1500 (F3), and this formulation had the highest drug release in 30 min along with a DE% of 93.5%. This was followed by suppositories with a blend of PEGs (F5), which had a DE% of 90.9%. The high release rate of MEO from PEG suppository bases (F3 and F5) may be the result of the opposite natures of the aqueous base and the fatty nature of the active material. However, users may experience slight irritation when using PEG-based suppositories.

Slow and incomplete release in 30 min was observed with Suppocire fatty bases, *i.e.* DE% of 56.8% with Suppocire AML (F1) and DE% of 12.5% with Suppocire CM (F2). The slow and incomplete release

Table 7. Disintegration time, percentage dissolution efficiency, and fracture points of different suppositories

Formulations	Disintegration time (min)	Dissolution efficiency (%)	Fracture point (kg)
F1	1.5	56.8	0.7
F2	2.0	12.5	0.9
F3	2.5	93.5	2.4
F4	15.0	85.6	3.0
F5	7.0	90.9	3.2
F6	2.0	85.5	1.7
F7	5.0	33.4	1.0

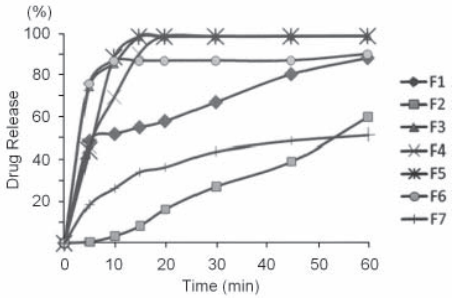

Figure 1. Mean drug release from different suppository formulations (F1-F7). Drug release was examined in phosphate buffer, pH 7.4, with 3% sodium lauryl sulphate maintained at 37 ± 0.5°C (n = 3).

of the MEO from Suppocire-based suppositories F1 and F2, despite their quick disintegration time, may be attributed to the high affinity of the oily active material for the fatty base, presumably hindering its release (*18*).

A mixed fatty/water-soluble suppository base containing 70% PEG 1500 and 30% Suppocire CM produced poor results, which may be attributed to the entrapment of MEO in the fatty Suppocire component. In a previous study, drugs such as Etodolac produced good results with this base (*28*). This may be explained by the state in which the drug is dispersed in the base. MEO is a hydrophobic liquid and therefore may undergo quick and extensive distribution in the fatty Suppocire component. This would hinder its departure from the suppository base and entry into the dissolution medium.

4. **Conclusion**

A stable MEO emulsion with an acceptable taste was formulated using Cremophore as an emulsifier and a combination of anise oil, peppermint oil, and glycerol as flavoring agents. Masking of the bitter and disagreeable taste of MEO will improve patient acceptance and compliance. Suppositories prepared from PEG 1500 (F3) yielded satisfactory results as evidenced by more than 90% release after 30 min.

Suppository formulations containing fat-soluble Suppocire AML and CM had poor release properties. Suppositories with mixed water and fat-soluble bases (PEG 1500:Suppocire CM; 70 and 30%) had inferior release properties in comparison to those based only on PEGs.

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