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FORMULATION AND IN-VITRO EVALUATION OF HALOPERIDOL SOLID DISPERSION INCORPORATED INTO RECTAL SUPPOSITORIES

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ABSTRACT:

The potential of solid dispersion (SD) technique to improve the dissolution of haloperidol (Hal) and to develop Hal rectal suppository was investigated. Hal solid dispersions with hydrophilic carriers, namely, polyethylene glycol 6000 (PEG 6000) or sodium starch glycolate (SSG) in different mixing ratios were prepared by kneading technique. Dissolution studies in phosphate buffer pH 7.4 using USP paddle method were performed for Hal and its physical mixtures and solid dispersions. Fourier-transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), and X-ray powder diffraction (XRD) analysis were performed to identify the physicochemical interactions between the drug and carrier, hence its effect on dissolution. Hal suppositories were prepared using water soluble base, polyethylene glycol (PEG 6000, 40% w/w and PEG 400, 60% w/w) and oleaginous base (Witepsol H15) utilizing molding technique. The prepared suppositories were tested for hardness, melting time, weight variation and drug content. All these properties were found to be satisfactory for practical use. The dissolution of Hal was improved significantly from its kneaded products with both carriers. Highest dissolution rate of the drug was obtained from Hal solid dispersions at the mixing ratio of 1:7 drug: carriers ratios. SSG was superior in dissolution enhancement of Hal from its solid dispersion. FTIR spectra suggested the presence of hydrogen bonds between the carriers' hydroxyl groups and the drug. Powder-XRD technique in combination with differential scanning calorimetry revealed that Hal existed in crystalline form in PEG and SSG polymers. Drug release from the water soluble suppository base was greater than that from oleaginous base. Maximum drug release was obtained from suppositories containing water soluble base incorporated with Hal solid dispersion.

INTRODUCTION

Rectal route is the simplest alternative to the oral route particularly in very young, elderly, nauseous, postoperative and mentally disturbed patients. Dreifuss et al[1] reported that rectal diazepam gel, administered at home by trained care givers, is an effective and well tolerated treatment for acute repetitive seizures. In contrast to oral dosage forms, more than 75% of intact drug can be absorbed into blood circulation without passing liver in suppository form[2,3]. Chemically, haloperidol (Hal) is 4-[4-(p-chlorophenyl)-4-hydroxypiperidino]-4'-fluorobutyrophenone. The trademark of the manufactured dosage form is (Haldol®). It is used in treatment of psychiatric disorders and exhibits potent antiemetic properties in small doses[4,5]. Hal has a number of potential benefits for the prevention of postoperative nausea and vomiting related to neuraxial opioids, including dopamine receptor antagonism at the chemoreceptor trigger zone[6-9], long half-life[10-12], small cost, and infrequent incidence of side effects when used at doses smaller than those used for antipsychotic treatment[4,5]. Also, Hal is effective in prophylaxis of cancer chemotherapy-induced emesis[13]. However, no rectal dosage form of haloperidol is available. Since haloperidol has poor aqueous solubility (< 0.01g/100 ml 25°C)[14], its slow release from suppository formulations may be anticipated. Solid dispersion technique has been used for a wide variety of poorly aqueous soluble drugs such as nimesulide[15], ketoprofen[16], tenoxicam[17], nifedipine[18], nimodipine[19], ursodeoxycholic acid[20] and albendazole[21] for improvement of their dissolution characteristics and bioavailability. Solid dispersion, which was introduced in the early 1970s[22], is essentially a multi-component system, having drug dispersed in and around hydrophilic carrier(s) such as polyethylene glycols[23], polyvinylpyrrolidone[24], hydroxypropyl methylcellulose[25], gums[15], sugar[26], mannitol[27], urea[20], and superdisintegrants such as sodium starch glycolate[28,29]. The solvent evaporation[30], melt adsorption[31], fusion[32], spray drying[33], spray freezing[34], spray congealing[35], melt extrusion[36], supercritical fluid precipitation[37] and kneading[38] are the techniques reported for the preparation of solid dispersions. Different attempts were made to improve the release property of poorly water-soluble drugs from suppository bases by means of solid dispersions techniques[39-41]. Therefore, the present investigation aimed to develop a novel Hal rectal drug delivery system containing its solid dispersion with different hydrophilic carriers using various suppository bases.

MATERIALS AND METHODS

Materials

Haloperidol (Hal) was obtained from Janssen-Cilag Company, scientific office, Nasr City Egypt. Polyethylene glycol 400 (PEG400), polyethylene glycol 6000 (PEG6000), and sodium starch glycolate (SSG) were kindly provided by Egyptian International Pharmaceutical Industries Company, Tenth of Ramadan City, Egypt. Witepsol H15 was obtained from Memphes Pharmaceuticals Co., Egypt. All reagents and solvents used were of analytical grade.

Methods

Preparation of Solid Dispersions

A mixture of carriers and Hal (1:2, 1:5, 1:7, and 1:9 by weight) was wetted with 1 ml of water and kneaded thoroughly for 30 minutes in a glass mortar. The paste formed was dried under vacuum for 24 hours. Dried powder was passed through a sieve no. 60 and stored in closed vials for further evaluation. Physical mixtures (PM) were obtained by mixing in a glass

mortar accurately weighted amount of Hal and the carriers in a respective ratio as the solid dispersion.

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra were obtained on a Perkin-Elmer 1600 FTIR spectrophotometer Perkin-Elmer, Inc., Norwalk, USA) using potassium bromide disk method. The scanning range was 400-4000 cm^{-1} and the resolution was one cm^{-1}.

Differential Scanning Calorimetry (DSC)

The DSC thermograms were recorded on a Shimadzu differential scanning calorimeter (Shimadzu, Japan). Samples of 1.6-2 mg weight were heated in hermetically sealed aluminum pans over a temperature range of 30-200°C at a constant rate of 10°C/min under nitrogen purge (20 ml/min.).

X-Ray Diffraction (XRD)

X-ray diffraction patterns were obtained using a scintag XGEN 4000 powder diffractometer (XGEN 4000, advanced diffraction system, Scintag Inc., USA) with CuKα radiation. Diffractograms were run at a scanning over a 2θ range of 4-80°.

Solubility Studies

An excess of Hal was added to screw-capped vials containing aqueous polymer solution (0.05% to 0.25% w/v concentration range). Vials were shaken mechanically at 25 ± 0.5°C for 24 hours. At equilibrium after 2 days, aliquots were withdrawn, filtered through a millipore membrane filter (0.22 µm pore size) and spectrophotometrically assayed for drug content at 243 nm (Shimadzu-UV 160A Spectrophotometer). Each experiment was performed in triplicate.

Dissolution Studies

Dissolution rate studies were performed using 6-station USP XXII apparatus (Pharma Test sp-400, Germany) with paddle rotating at 100 rpm in phosphate buffer (pH 7.4) at 37 ± 0.5°C. Pure drug (10 mg) and powdered solid dispersions as well as physical mixtures, each containing 10 mg of drug were subjected to dissolution. At fixed time intervals, samples withdrawn were filtered and spectrophotometrically assayed for drug content at 243 nm. Each test was performed in triplicate. The dissolution profiles of Hal were examined using the following parameters: 1) the initial dissolution rate in 15 min (IDR_{15}) that was calculated as percent dissolved of the drug over the first 15 min/min. 2) the percentage of the drug dissolved after 15 and 60 minutes (PD_{15} and PD_{60}), and 3) the dissolution efficiency of the drug (DE_{60}%) which was measured from the area under the dissolution curve for 60 min (measured using the trapezoidal rule) and expressed as percentage of the area of the rectangle described by 100% dissolution in the same time[42].

Preparation of Haloperidol Suppositories

Hal suppositories containing 10 mg of the raw drug or its equivalent from kneaded products were prepared by the fusion method using a metal mould with six cavities. The suppository bases employed were a blend of polyethylene glycols (PEG 6000, 40% w/w and PEG 400, 60% w/w) and Witepsol H15. Drug displacement values of the bases used were first determined and the amount of drug required was calculated. After the suppositories were solidified at room temperature, they were stored at 4°C. The suppositories were separately weighed and the mean weight was calculated.

Technical Assays

Six suppositories were separately weighed and the mean weight was calculated. The liquefaction time was determined by warping the suppository in a dialysis membrane and placed in a beaker containing 100 ml phosphate buffer pH7.4 at 37±1 °C and shaken in a water bath 100 rpm. The time of complete melting of the suppositories was recorded in minutes[43]. The tablet hardness tester (Pharma Test tablet hardness tester, Germany) was used to measure the resistance of the suppositories to crushing (fragility or brittleness). The hardness of a cylindrical sample (8 mm thickness) which was obtained by cutting the middle portion of a suppository was measured in its diameter direction[41].

Determination of Content Uniformity

Six suppositories were weight and tested for drug content by dispersing the suppositories individually in 250 ml capacity conical flask containing 100 ml 0.1N HCl, with heating and shaking. The clear filtered solutions were measured spectrophotometrically, after appropriate dilution, against blank.

In Vitro Drugs Release from Suppository Formulations

In vitro release of Hal from the suppositories was carried out using a modified USP XXII paddle. Suppositories were placed in a wire mesh basket and introduced at the bottom of the beaker. Sorensen's phosphate buffer (900 ml) with pH 7.4 at 37°C ± 0.5°C was used as the release medium. The rate of stirring was 100 rpm. At predetermined intervals, 5ml of the release medium was collected and filtered. The release medium was then replaced with 5 ml of fresh buffer to maintain a constant volume. Hal content in the release medium was determined by a spectrophotometer at 243 nm. The mean of three determinations was used to calculate the drug release from each formula.

RESULTS AND DISCUSSION

Solubility Studies

Solubility data for raw Hal in water and in presence of different percentages of the PEG6000 and SSG is given in Table 1. The solubility of the drug increased as the carriers concentrations increased. PEG 6000 was more efficient for improving Hal solubility. For instance, addition of either PEG6000 or SSG increased the solubility of the drug by 2.8 and 1.3 times at 0.25% carriers' concentration, respectively. The improved solubility of Hal in the carriers' solutions may be attributed to the carriers' surface activity. The

hydrophilic carriers increase the drug wettability by decreasing the interfacial tension between the solid drug particles and water[44].

Table (1): Solubility data of haloperidol in water in presence of different concentrations of polyethylene glycol and sodium starch glycolate at 25°C

Polymer concentration g%	Solubility µg/ml (mean ±SD)	
	PEG6000	SSG
0	36.1±3.2	36.1±3.2
0.05	38.8±2.2	35.21±2.2
0.10	54.19±2.7	34.11±3.1
0.15	62.77±3.5	39.83±2.1
0.20	73.58±4.6	40.8±1.2
0.25	101.55±3.7	46.88±2.3

Dissolution Rate Studies

Dissolution profiles of the raw powdered Hal and its carrier binary systems are presented in Figures 1 and 2. It is evident that the solid dispersion (SD) technique using kneading method improved the dissolution rate of Hal to a great extent compared to raw Hal and PM. During dissolution studies, it was noted that drug-carrier systems sink immediately, whereas pure drug keeps floating on the surface for a longer time. A similar result was observed by Mody and Tayade[38].Tables 2 and 3 summarize the calculated dissolution parameters for Hal and its binary systems with carriers. All Hal preparations exhibited fast initial dissolution rate within the first 15 min. Raw Hal yielded the slowest dissolution rate. For example 4.72±1.0% and 8.48±1.54% were dissolved from the powdered raw Hal after 15 and 60 min, respectively. This result could be ascribed to the hydrophobic nature of the raw Hal powder. Physical mixtures (PM) improve dissolution rate of the drug by a significant extent ($P < 0.05$). For example, the amount of Hal dissolved after 60 min were 26.32±0.68% and 25.59±1.92% from PMs containing 1:7 Hal: PEG6000 or SSG, respectively. Compared with raw powder, Hal solid dispersion with either PEG6000 or SSG exhibited enhanced dissolution. IDR_{15} and DE_{60} increased with increasing concentration of the carriers till optimum carriers' concentration (1:7 drug:carriers' ratio). Hal:SSG solid dispersion in a mixing ratio 1:7 shows maximum enhancement in dissolution rate (PD_{60} = 71.5%). The order of efficiencies of products based on DE_{60} values is Hal:SSG SD > Hal:PEG SD > Hal:SSG PM = Hal:PEG PM > Hal. The significant enhancement of dissolution of Hal from drug-carrier systems could be attributed to higher wettability and dispersibility of the drug. Ford[45] reviewed the mechanism of dissolution rate improvement from solid dispersions. Lack of crystallinity, ie, amorphization, increased wettability and dispersibility and particle size reduction considered to be important factors for dissolution rate enhancement. In the present investigation it could be speculated that dry mixing of Hal with a hydrophilic carriers result in greater wetting of the drug and increases surface available for dissolution by reducing interfacial tension between the hydrophobic drug and dissolution media.

Table (2): Dissolution parameters (± SD) of haloperidol from different haloperidol Polyethylene glycol 6000 (PEG6) systems in phosphate buffer (pH 7.4).

		IDR (%/min)	PD_{15} (%)	PD_{60} (%)	DE_{60} %*10^{-2}
Haloperidol		0.32 ±0.07	4.72 ±1.00	8.48 ±1.54	5.35 ±1.6
Physical mixtures (Drug:PEG6)	1:2	0.873 ±0.071	13.09 ±1.07	17.88 ±0.11	13.11 ±1.28
	1:5	1.103 ±0.202	16.55 ±2.03	23.30 ±1.48	17.21 ±1.80
	1:7	1.246 ±0.102	19.28 ±1.53	26.32 ±0.68	18.73 ±1.69
	1:9	1.215 ±0.173	18.22 ±2.60	23.69 ±0.86	18.64 ±1.20
Solid dispersion (Drug:PEG6)	1:2	1.304 ±0.173	19.56 ±2.67	33.53 ±1.41	23.50 ±1.80
	1:5	2.385 ±0.232	35.27 ±3.485	51.20 ±1.86	38.93 ±1.99
	1:7	3.033 ±0.207	45.50 ±3.110	54.30 ±2.339	45.38 ±3.60
	1:9	2.425 ±0.172	36.37 ±2.579	52.12 ±0.415	40.87 ±1.70

Table (3): Dissolution parameters (± SD) of haloperidol from different haloperidol sodium starch glycolate (SSG) systems in phosphate buffer (pH 7.4).

		IDR (%/min)	PD_{15} (%)	PD_{60} (%)	DE_{60} %*10^{-2}
Haloperidol		0.32 ±0.07	4.72 ±1.00	8.48 ±1.54	5.35 ±1.6
Physical mixtures (Drug:SSG)	1:2	0.706 ±0.144	10.62 ±2.15	22.03 ±0.674	13.55 ±1.17
	1:5	1.227 ±0.056	18.40 ±0.832	23.16 ±2.843	18.47 ±1.18
	1:7	1.174 ±0.107	17.61 ±1.601	25.59 ±1.923	19.71 ±2.20
	1:9	1.075 ±0.088	16.05 ±1.327	23.16 ±0.968	17.82 ±0.99
Solid dispersion (Drug:SSG)	1:2	3.535 ±0.092	20.66 ±1.385	32.2 ±1.762	50.60 ±1.07
	1:5	4.102 ±0.024	32.20 ±0.361	52.68 ±0.511	58.23 ±1.56
	1:7	4.844 ±0.227	51.60 ±3.412	71.50 ±1.159	68.91 ±3.29
	1:9	4.521 ±0.158	47.36 ±3.372	62.53 ±2.598	64.98 ±2.69

The kneading process resulted in a uniform distribution of drug in the carrier crust in a highly dispersed state. Thus, when such a system comes in contact with an aqueous dissolution medium, the hydrophilic carrier dissolves and results in precipitation of the embedded drug into fine particles, which increase the dissolution surface available. The remarkable dissolution enhancement of Hal from Hal:SSG (1:7) solid dispersion could be attributed to the water swellable nature of the SSG[46]. It holds the

drug in an intimate contact with water, owing to its water retention potential, and increases the drug wetability. In order to understand the mechanism of dissolution enhancement of Hal from PMs and SDs, the investigated systems were also characterized by fourier transform infrared (FTIR) spectroscopy, differential scanning calorimetry (DSC) and X-ray diffraction (XRD).

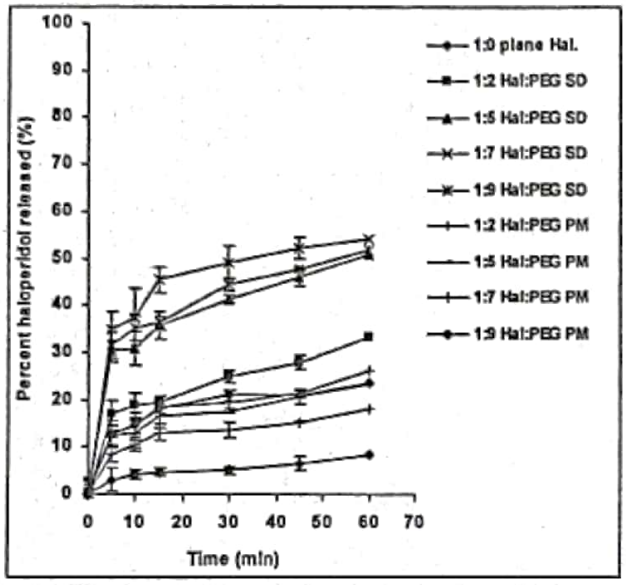

Figure (1): Dissolution profiles of haloperidol from different haloperidol-PEG6000 systems prepared by kneading in phosphate buffer pH 7.4.

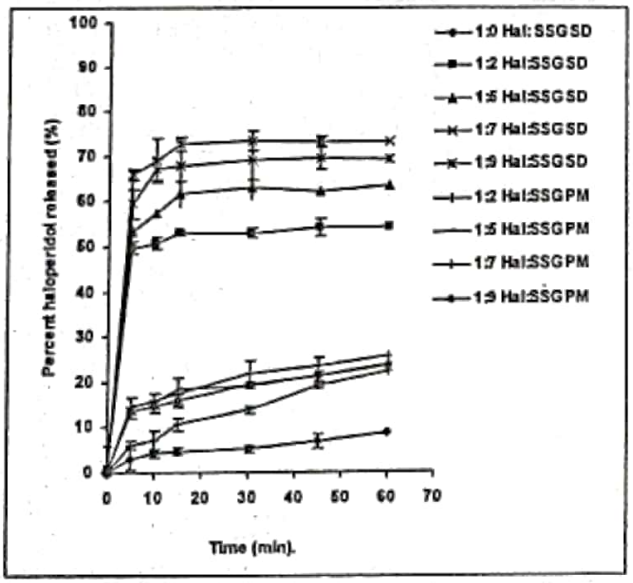

Figure (2): Dissolution profiles of haloperidol from different haloperidol-Sodium starch glycolate systems prepared by kneading in phosphate buffer pH 7.4.

Fourier Transform Infrared (FTIR) Spectroscopy

FTIR spectroscopy was performed to investigate the presence of an interaction between Hal and the carriers used. The spectra of Hal, carriers, physical mixture and solid dispersions are shown in Figures 3 and 4. FTIR spectra of raw Hal showed characteristic bands at 3128 cm^{-1} (O-H stretching), 2828 cm^{-1} (C-H aliphatic stretching), two characteristic intense bands at 1681 cm^{-1} (C=O stretching) and 1596 cm^{-1} (C=C aromatic), and 1220 cm^{-1} (C-OH stretching vibration). A medium intensity peak at 828 cm^{-1} was also assigned to –CH deformation of p-substituted aromatic ring. PEG 6000 spectra exhibited a broad band at 3446 cm^{-1} characteristic for terminal O-H stretching vibration and a strong band at 2887 cm^{-1} corresponding to C-H stretching of OC_2H_4 group. Spectra of Hal PM with PEG6000 showed that the O-H stretching vibration band of PEG6000 at 3446cm^{-1} decreased in intensity with a significant shift to a lower wave number. However, the spectrum of the SD of Hal with PEG showed disappearance of this band. This result suggests a possibility of intermolecular hydrogen bonding between the O-H group of PEG6000 and the F, Cl or O-H of the drug molecule. SSG spectra showed a significant broad and large band at 3650-3150 cm^{-1} for free O-H stretching vibration. This band showed a reduction in intensity and a shift to lower wave number in SSG physical mixture with Hal. Spectra of Hal-SSG SD showed disappearance of O-H band exhibited by the SSG. Similarly, this observation suggested that some sort of intermolecular hydrogen bonding existed between the O-H group of the SSG and the F, Cl or O-H of the drug. Previous studies reported that the shift or disappearance of different characteristic band in FTIR spectra was attributed to solid-state hydrogen bonding between drugs and the carriers[47,48]. From the FTIR results, it can be concluded that drug-carrier hydrogen bonding existed in the binary system that may cause a reduction in drug recrystallization[49].

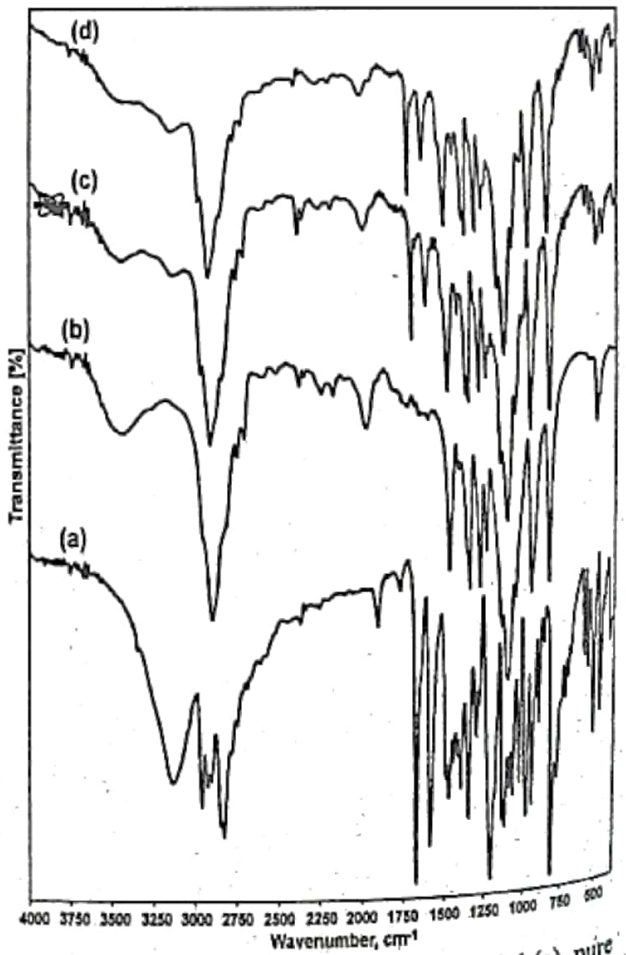

Figure (3): FTIR spectra of pure haloperidol (a), pure PEG6000 (b), 1:2 Hal-PEG physical mixture (c) and 1:2 Hal-PEG solid dispersion (d)

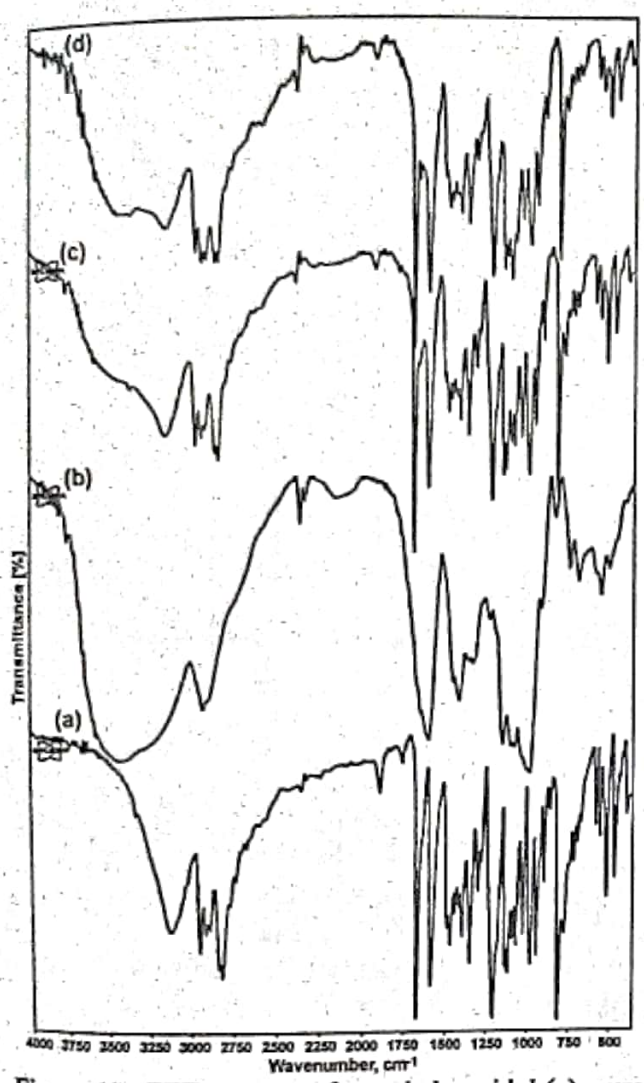

Figure (4): FTIR spectra of pure haloperidol (a), pure SSG (b), 1:2 Hal-SSG physical mixture (c) and 1:2 Hal-SSG solid dispersion (d)

Differential Scanning Calorimetry (DSC)

The thermal behavior of the individual components and the binary systems of Hal with either PEG6000 or SSG are depicted in Figures 5 and 6, respectively. The DSC thermogram of raw Hal showed a single sharp endothermic peak at 152.09°C corresponding to its melting, indicating its crystalline nature. The thermogram of PEG6000 showed a single endothermic peak at 60.75°C corresponding to its melting point. The thermogram of SSG carrier exhibited a single, very broad endothermic peak at 50-100 °C. This peak corresponds to the water released from the SSG powder. The endothermic transition of Hal was broadened and shifted towards a lower temperature in the spectra of its systems with PEG6000. This could be attributed to higher polymer concentration and uniform distribution of drug in the crust of polymer, resulting in complete miscibility of drug in molten polymer[50-52]. In contrast, the thermogram of Hal PM with SSG showed sharp intense peak at 151.13°C corresponding to Hal fusion. However, its SD thermogram showed a broadening of this peak signifying that its solubility in SSG is relatively high.

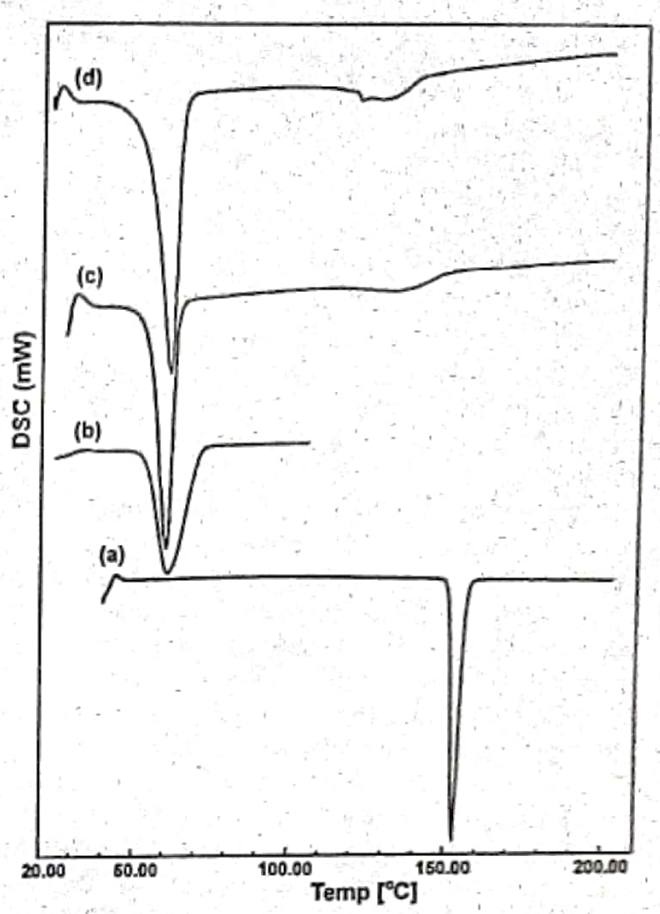

Figure (5): DSC thermograms of pure haloperidol (a), pure PEG6000 (b), 1:2 Hal-PEG physical mixture (c) and 1:2 Hal-PEG solid dispersion (d)

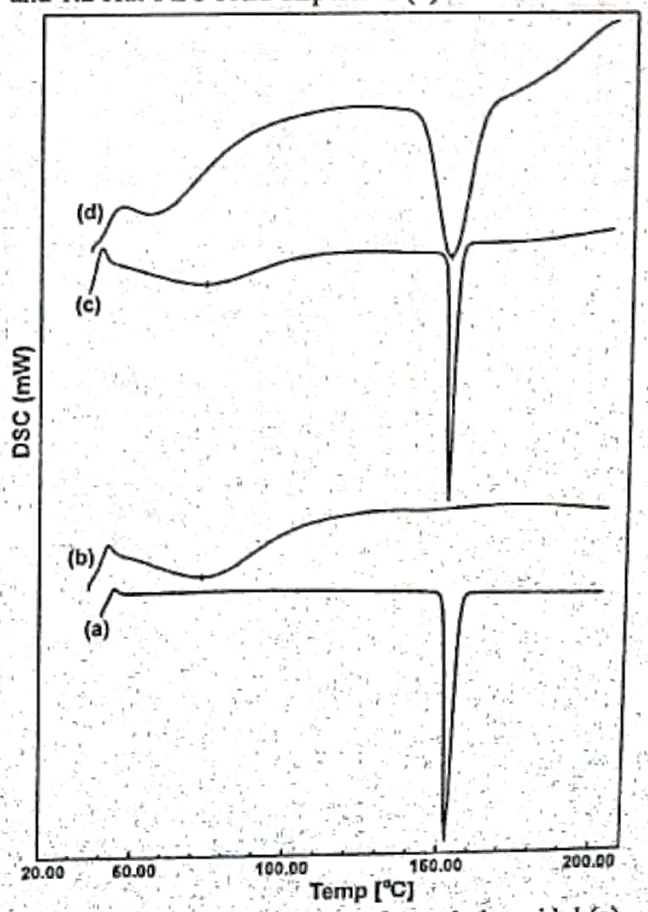

Figure (6): DSC thermograms of pure haloperidol (a), pure SSG (b), 1:2 Hal-SSG physical mixture (c) and 1:2 Hal-SSG solid dispersion (d)

X-Ray Diffraction (XRD)

XRD patterns of Hal, PEG6000, SSG, and their PM and SD are shown in Figures 7 and 8. XRD analysis of raw Hal exhibited characteristic intense diffraction peaks of Hal appeared at a diffraction angles of (2θ) at 6.41°, 11.56°, 12.78°, 14.74°, 19.57°, 22.5°9, 24.52°, 26.1°, 27.8°, and 29.57° indicating a typical crystalline pattern. XRD patterns of PEG showed two characteristic peaks of high intensity at 18.98° and 23.12°. SSG had a higher intensity peak at 45.29° in addition to relatively lower intensity peaks at 21.98°, 31.62°,38.1°, 56.46° and a hallow pattern at 5-19°. Hal binary systems with either PEG6000 or SSG possessed the diffraction peaks of both drug and carrier, indicating the crystalline state of Hal. However, the intensity of SSG peak at 45.29° in PM and SD was significantly reduced. This may indicate minor changes in the crystallinity of SSG. The obtained results are in a good agreement with those obtained from the FTIR and DSC analysis. This could indicate that the potential of the investigated carriers to increase the dissolution of Hal from their binary systems is due to the chemical interaction rather than the change in the drug crystallinity.

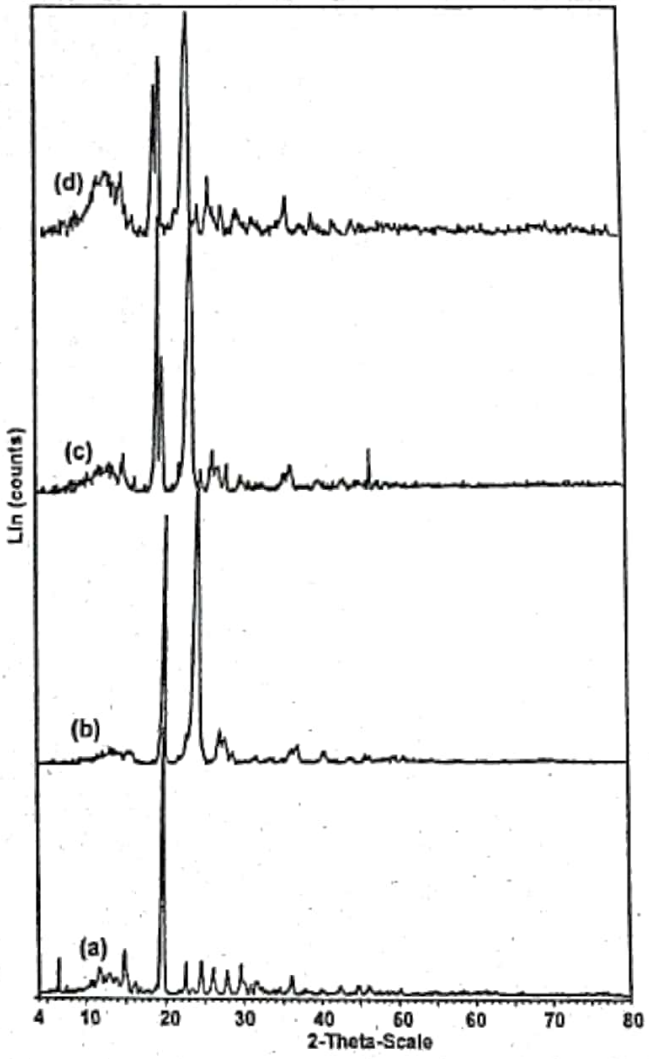

Figure (7): X-ray defractograms of pure haloperidol (a), pure PEG6000 (b), Hal-PEG physical mixture (c)and Hal-PEG solid dispersion (d)

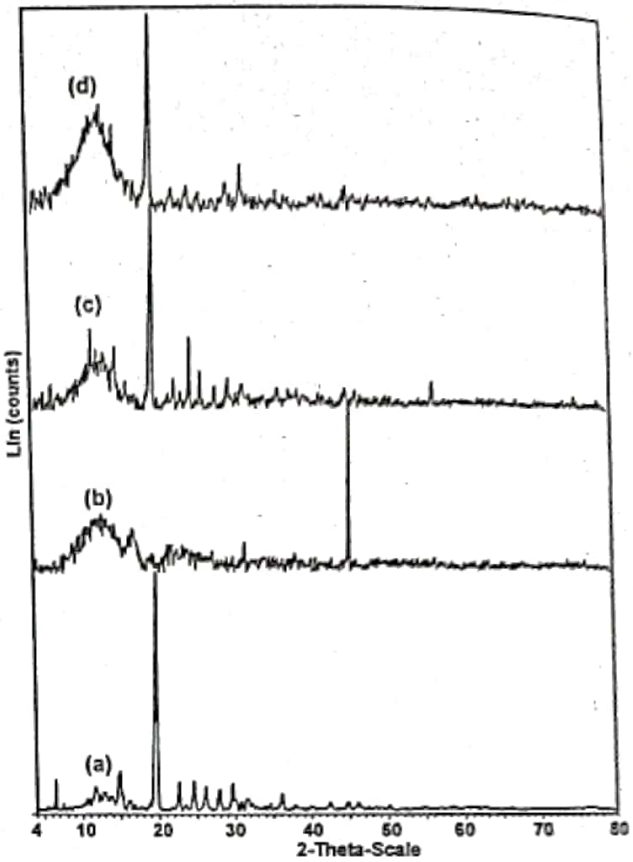

Figure (8): X-ray defractograms of pure haloperidol (a), pure SSG (b), Hal-SSG physical mixture (c)and Hal-SSG solid dispersion (d)

Release of Haloperidol from Suppositories

The potential of suppository bases, water soluble (PEG) and oleaginous (Witepsol H15) bases, in developing Hal rectal dosage forms was investigated. The pharmaceutical quality control assessment of suppositories containing raw Hal and its SD either with PEG6000 or SSG are presented in Table 4.

Table (4): Properties of different haloperidol suppository formulations (n=6)

Suppository Formulations	Weight variations (g) ±SD	Liquification time (min) ±SD	Hardness (Kps) ±SD	Content uniformity (%) ±SD
PEG	1.217 ±0.028	25 ±2.0	2.2	0
Witp	1.003 ±0.009	4.0 ±1.0	1.8	0
Hal -PEG	1.205 ±0.027	10 ±0.45	1.9	94.18 ±4.6
Hal-Witp	0.991 ±0.007	7.30 ±0.22	1.8	95.63 ±0.9
PEG6-SD-PEG	1.189 ±0.025	15 ±0.51	2.0	94.68 ±1.2
SSG-SD-PEG	1.209 ±0.053	17.2 ±0.52	2.1	97.50 ±2.5
PEG6-SD-Witp.	1.008 ±0.029	5.5 ±0.55	1.9	96.89 ±2.4
SSG-SD-Witp	1.051 ±0.023	6.3 ±0.53	1.8	94.88 ±2.3

All the tests complied with the pharmacopoeial standards. Considering the hardness of suppositories, all the formulas tolerated more than 1.8 Kg. The mechanical strength of suppositories should in no case be less than 1.8-2 Kg[53]. The effect of changing the suppository bases on the extents and rates of release of Hal from its formulations is shown in Table 5.

Table (5): Dissolution parameters (± SD) of haloperidol from different suppository formulations in phosphate buffer 7.4.

Suppository formulation	IDR (%/min)	PD_{15} (%)	PD_{60} (%)	DE_{60} %*10^{-2}
Hal-PEG	3.32 ±0.17	36.63 ±5.94	45.51 ±5.20	45.37 ±2.18
Hal-Witp	1.01 ±0.14	3.48 ±1.84	9.42 ±1.58	13.58 ±2.01
PEG6-SD-PEG	4.23 ±0.28	44.36 ±6.65	62.11 ±1.53	57.68 ±3.73
SSG-SD-PEG	4.07 ±0.33	38.10 ±5.02	56.65 ±3.10	52.10 ±4.56
PEG6-SD-Witp.	1.99 ±0.05	8.91 ±0.41	21.21 ±2.82	27.60 ±1.72
SSG-SD-Witp	2.81 ±0.04	12.84 ±0.93	27.47 ±0.52	35.21 ±1.18

Hal release profiles from the prepared suppositories are depicted in Figure 9. The release rate and DE_{60} of Hal were significantly higher from PEG base than from Witepsol H15 ($P<0.05$). This could be attributed to the fact that Hal is a lipophilic drug and its solubility in hydrophilic bases is expected to be low. Consequently, the drug has a higher tendency to diffuse out of hydrophilic bases. Another important factor that can influence the drug release is the water-absorbing property of the base which can facilitate penetration of the dissolution medium into the base with subsequent wetting and desorption of the embedded drug. The literature abounds with reports on improvement of dissolution of poorly water-soluble drugs from polyethylene glycol - based solid formulations due to its water-absorbing properties[54,55]. Polyethylene glycol was found to be an optimal base for the formulation of suppositories containing poorly water soluble drugs[56-58]. In this investigation PEG suppository base incorporating raw Hal (Table 4) showed DE_{60} (45.5%) equivalent to that of Hal: PEG6000 (1:7) SD (Table 2). This can be attributed to formation of solid dispersion of Hal in PEG base during the melt-fusion stage of suppository preparation[59,60]. In addition, the dissolution rates of Hal from its solid dispersion incorporated suppositories were significantly improved compared to that obtained when raw drug was incorporated into suppositories. PEG suppository containing Hal:PEG6000 (1:7) SD showed the highest drug release followed by PEG suppository containing Hal:SSG (1:7) SD.

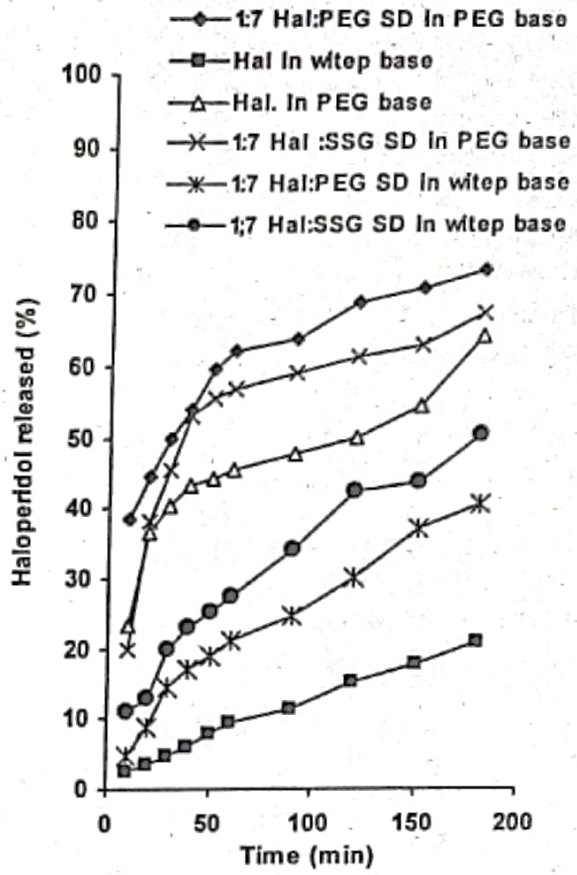

Figure (9): Release profiles of haloperidol from PEG and Witepsol H15 suppository bases containing pure haloperidol and Hal-PEG and Hal-SSG solid dispersions in phosphate buffer pH 7.4.

CONCLUSION

The study shows that the dissolution rate of Hal was enhanced to a great extent from its solid dispersion with hydrophilic carriers (PEG6000 or SSG). The water soluble base (PEG) was superior to the oleaginous base (Witepsol H15) in terms of its ability to release Hal from the suppository formulation. Hence, Hal-Hydrophilic carrier's solid dispersions along with use of water soluble base could be considered as an approach for Hal rectal dosage forms. For future prospects, in vivo bioavailability and bioequivalence studies will be conducted for the optimized haloperidol rectal suppository formulations.

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صياغة و تقييم معملي لعقار الهالوبيريدول في المشتتات الصلبة و المحملة في أقماع شرجيه

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يستعمل عقار الهالوبيريدول في علاج الحالات النفسية وله مفعول مضاد للقئ عند إستعماله بجرعات صغيرة، غير ان العقار لا يوجد في صورة اقماع شرجيه. وحيث أن العقار شحيح الذوبان في الماء فقد تم دراسة قدرة المشتتات الصلبة في تحسين معدل و سرعة ذوبان الهالوبيريدول في محلول الفوسفات المنظم للأس الهيدروجيني ٧،٤ . تم تحضير لمشتتات الصلبة للعقار مع نسب متعدده من الناقل لمحبة للماء مثل البولى ايثين جليكول ٦٠٠٠ أو صوديوم جليكولات النشا باستعمل طريقة العجن. وتم إجراء دراسة مقارنه عن مدي و معدل ذوبان الهالوبيريدول من كل من لخليط لطبيعي للعقار مع الناقل لمحبة للماء ومشتتته لصلبة. وتتم إستعمل جهاز الأشعة تحت لحمراء و جهاز تفريق أشعة لكس وكذلك جهاز لمسح لحراري لتفاضلى لدراسة لتأثير لطبيعي و لكيميائي الناقل لمحبة للماء علي لعقار في مستحضراته و ما يعكسه ذلك علي مدي و معدل ذوبان الهالوبيريدول من هذه المستحضرات. كذلك تم تحضير الأقماع الشرجية باستخدام قاعدتين أحداهما قاعدة تذوب في الماء و هى عبارة عن خليط من البولى ايثين جليكول ٦٠٠٠ (٤٠%) والبولى ايثين جليكول ٤٠٠ (٦٠%) و الأخرى قاعدة دهنية و هي ويتبسول اس ١٥. وقد بينت لفحوص لضبطة لجودة لمستحضرات الأقماع لشرجية (الاختلاف الوزني- وقت الانصهار -النسبة المئوية للعقار في القمع - درجة لصلابة) مطابقتها للمواصفات القياسية.

وقد أسفرت دراسات معدل ذوبان لعقار في محلول الفوسفات المنظم للأس الهيدروجين ٧،٤ عن وجود تحسن ملحوظ في مدي و معدل ذوبان الهالوبيريدول من لمشتتات لصلبة عند مقارنتها بمعدل ذوبان لعقار منفردا. كما اعطت لمشتتات لصلبة للهالوبيريدول و لمعد بنسبة ١:٧ بين لعقار و لناقل لمحبة للماء اعلي معدل لذوبان لعقار. وقد أظهرت لدراسة أيضا أن صوديوم جليكولات النشا له تأثير أفضل من البولى ايثين جليكول٦٠٠٠ علي مدى ومعدل ذوبان الهالوبيريدول من لمشتتات لصلبة كما اوضحت أطياف لمتصاص الأشعة تحت لحمراء عن وجود روابط هيدروجينيه بين مجموعة ليدروكسيل لموجوده في لناقل لمحبة للماء و لعقار. وكذلك أظهرت فحوصات تفريق أشعة لكس ولمسح لحراري لتفاضلي عن وجود لعقار في صورته لبلورية داخل لناقل لمحبة للماء. وقد بينت لتجارب لمعملية لإنطلاق لعقار من الأقماع الشرجية أن معدل انطلاق الهالوبيريدول من قاعدة الأقماع لتي تذوب في لماء (البولى ايثين جليكول) أفضل من قاعدة الأقماع لدهنية (ويتبسول اس ١٥). وقد اعطت قاعدة الاقماع لشرجية لتي تذوب في لماء و تحتوي علي لمشتتات لصلبة ١:٧ (عقار: البولى ايثين جليكول ٦٠٠٠) أ فضل معدل لإنطلاق الهالوبيريدول.