PREPARATION AND CHARACTERIZATION OF ATROPINE SULFATE ORODISPERSIBLE TABLETS

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ABSTRACT

The oral route of administration is considered as the most widely accepted route. The unique environment of the oral cavity offers its potential as a site for drug delivery. The objective of the current study was to formulate and evaluate an atropine sulfate (AS) orodispersible tablet (ODT) as an alternative non-invasive and portable dosage form for treatment of various emergency health conditions as treatment of organophosphate (OP) toxicity. Atropine sulfate auto injector, AtroPen®, is the only self-administered dosage form available as an antidote for out-of-hospital emergency use, but it is associated with several limitations and drawbacks. Nine formulations of atropine sulfate orodispersible tablets (F1 to F9) were prepared using different superdisintegrants, namely sodium starch glycolate, crosspovidone, crosscarmellose sodium with different concentrations (3, 5, and 8 %). The compatibility studies of drug and excipients were performed by Fourier transform infrared spectroscopy (FTIR) and differential scanning colorimetry (DSC). The final blend of the drug and excipients were evaluated for powder flow properties such as bulk density, tapped density, compressibility index, Hausner's ratio, and angle of repose. All nine formulations were evaluated for post-compression parameters such as thickness, weight variation, hardness, friability, drug content, disintegration time, wetting time, and in vitro dissolution studies. It was found that F9 had the best results as it had short disintegration time (11 sec) and wetting time (24.8 sec) with 102.22% drug release after 2 minutes. F9 was subjected to an accelerated stability study for 3 months, which showed no significant changes in all physicochemical parameters.

Keywords: Atropine Sulfate (AS), Orodispersible tablets (ODT), Organophosphate (OP), crosspovidone, sodium starch glycolate, crosscarmellose sodium, and direct compression.

Introduction

Oral route is one of the most frequently drug administration route since it is safe, easy to use, and results in high patient compliance **(Gulsun et al., 2017)**. Orodispersible tablets (ODTs) are oral solid dosage forms that dissolve and disintegrate quickly, and they don't require water to be used **(Olmez and Vural, 2009)**. They offer several advantages over oral conventional tablets, including ease of administration, improved patient compliance, rapid onset of action, avoid first pass metabolism and suitability for patients with swallowing difficulties **(Hirani et al., 2009).**

The excipients used in ODT formulations often include superdisintegrant, flavoring agent, sweetener, binder, lubricant, and filler. Many techniques can be used for preparing ODT, such as Lyophilization, direct compression method, phase transition process, spray drying, melt granulation, molding, sublimation, mass extrusion, and cotton candy process **(Nagar et al., 2011)**. It was reported that direct compression method produces ODTs with high mechanical strength and stability at short processing time with low cost **(Ahmed et al., 2006).**

Organophosphates (OPs) are compounds that mainly derived from phosphoric acid. OPs have been used to produce pesticides and nerve agents. OPs compounds have the ability to irreversibly bind to acetylcholine esterase and prevent the breakdown of acetylcholine leads to overstimulation of both the muscarinic and nicotinic receptors **(Zhao and Yu S, 2013)**.

Atropine sulfate (AS) has alkaloid properties that are extracted from atropa belladonna. AS acts as a reversible non-specific antagonist of muscarinic receptors and antagonizes the effects of acetylcholine on tissues innervated by postganglionic cholinergic nerves **(Brown and Laiken, 2010)**. It is considered the first-line antidote for organophosphate toxicity **(Iyer et al., 2015)**.

AS is listed as the only parenteral treatment for OP poisoning in all medical guidelines. These recommendations involve starting with a 2 mg atropine sulfate dose after symptoms of OP toxicity have been appeared. AS dose should then be doubled every five minutes until the symptoms of OP toxicity have been disappeared **(Eddleston et al., 2008)**. Since there are several limitations that have been reported in several studies of auto injector devices that have been used to deliver different emergency medication **(Bentur et al., 2006)**, a new AS orodispersible tablet was accordingly formulated as an OP antidote. The newly prepared atropine sulfate orodispersible tablets would offer an alternative, non-invasive, user-friendly, and flexible dosage form for the potential treatment of OP toxicity that overcomes the drawbacks of administering AS using an auto injector and allows for early initiation of the treatment until patients are transported to a healthcare facility, which is critical in developing countries with high incidence rates but lake AS auto injectors.

Experimental

Materials

Atropine sulfate (AS) was kindly gifted by Orchidia pharmaceutical company (Obour City, Egypt). Mannitol (Spray dried SD2) was kindly gifted by Utopia Pharmaceuticals (Egypt). Microcrystalline cellulose (Avicel 102), sodium starch glycolate, Sucralose, crosscarmellose sodium, Crospovidone and Magnesium stearate were kindly gifted by Gypto Pharmaceutical Company (Cairo, Egypt). Solvents (distilled water, methanol) of HPLC analytical grade were purchased from Fisher Scientific Company (USA). Potassium phosphate monobasic was purchased from Alpha Chemika (India). Acetonitrile was purchased from LiChrosolv (Germany). Ethanol absolute (HPLC grade) was purchased from Merck (Germany). All other chemical were used of analytical grade.

Methodology

HPLC method for quantitation of atropine sulfate

UV scanning of atropine sulfate

An accurately weighed sample of 20 mg of atropine sulfate powder was dissolved in distilled water (HPLC grade) in 100 ml volumetric flask to give standard stock solution of 200 µg ml-1. The stock solution was then filtered and scanned using UV Spectrophotometer (Schimadzu, Japan) at range of 200 – 400 nm to get the wave length with maximum absorbance**(USP/NF, 2023)**.

Chromatographic system

A high performance liquid chromatography (HPLC) method was performed with some modification and validated for system selectivity, linearity, recovery, precision, accuracy. HPLC system was of model (Alliance), Waters2695 separation module, equipped with UV-VIS detector (waters 2996 PDA detector), C18 column (thermo hypersil BDS, 4.6* 150 mm/ 5 µm). The injection volume was 100 µL, flow rate 1.5 ml/ min, retention time approximately 3.6 min and run time 5 min. AS was measured at wavelength 210 nm in accordance with atropine sulfate monograph **(USP/NF, 2023)**.

Construction of calibration curve of atropine sulfate

Mobile phase was a mixture of potassium phosphate monobasic buffer: acetonitrile (85:15, V/V). In a series of 50-ml volumetric flasks, aliquots of different working standard solutions were transferred and diluted to volume with distilled water (HPLC grade), so the series of flasks contained (1, 2, 4, 4.8, 6 µg ml^{-1}) with distilled water. Each solution was sonicated for 30 min, and filtered through 0.45 µm syringe filter. Each solution was measured by HPLC using PDA UV-detector at the determined λ max 210 nm. A calibration graph was constructed by plotting peak area

versus the corresponding drug concentrations in μg ml^{-1} and the regression equation of the linear relationship was obtained.

Preformulation studies

Drug- excipient compatibility studies

Differential scanning calorimetry (DSC) studies

The compatibility of AS alone and AS with different excipient mixture was investigated using DSC (Schimadzu, Japan). Approximately 5 mg of samples were weighed and placed in the aluminum pans and heated at a rate of 10 °C/min, with indium in the reference pan under nitrogen at temperature 5-400°C **(Choudhary et al., 2012).**

Fourier-Transform Infrared Spectroscopy (FTIR) studies

Samples of 1-2 mg of AS alone, and As with a different physical mixtures with the investigated excipients; sodium starch glycolate, crosscarmellose sodium, crosspovidone, Avicel 102, and mannitol in a ratio of (1:1 W/W) were prepared by simple mixing. Samples were mixed with KBr (IR grade), compressed into discs in the compression unit under vacuum and scanned using FTIR (Schimadzu, Japan) from 4000-400 cm^{-1} with empty pellet holder as a reference **(Lai et al., 2011).**

Flowability studies of blended powder

A. Angle of repose (θ) studies

It is the maximum angle between the surface of the pile of powder and the horizontal plane. It is an indicative of the flow properties of the powder. It can be determined by using funnel method. The accurately weighed blend of 500 gm was taken in a funnel. The height of the funnel was adjusted in such a way until the tip of the funnel just touched the apex of the heap of blend. The diameter of the powder cone was measured and angle of repose was calculated using the following equation**.**

$$\text{Tan } \Theta = h/r \qquad (1)$$ **(B.P., 2009).**

Where, h and r are the height of cone and radius cone base, respectively.

B. Bulk density studies

Apparent bulk density is determined by pouring a weighed quantity of blend into graduated cylinder then measuring the volume and weight. Bulk density can be calculated by using following formula:

Bulk density = Weight of the powder / Volume of the packing (2) **(B.P., 2009)**

C. Tapped density studies

It was determined by placing a graduated cylinder, containing a known mass of drug-excipients blend. The cylinder was allowed to fall under its own weight onto a hard surface from the height of 10 cm at 2 second intervals. The tapping was continued until no further change in volume is noted. Tapped density can be calculated by using following formula:

Tapped Density = Weight of the powder / volume of the tapped packing (3) **(B.P., 2009)**

D. Compressibility index (Carr's Index) studies

The compressibility index of the blend was one of the sample methods to evaluate flow property of a powder by comparing the bulk density and tapped density. A useful empirical guide was given by the Carr's compressibility **(Lachman et al., 1990)**. Compressibility Index can be calculated by using following formula:

Compressibility Index (%) = [(TD-BD) X 100] / TD] (4) **(B.P., 2009).**

Where, TD = tapped density, BD = bulk density

E. Hausner's ratio studies

It provides an indication of the degree of densification which could result from vibration of the feed hopper and it was calculated as follow:

Hausner's ratio = (Tapped density x 100)/ (Poured density) (5) **(BP., 2009).**

Formulation of atropine sulfate orodispersible tablets

AS orodispersible tablets were prepared by direct compression method according to the formulae given in

Table 1. Nine formulations (F1 to F9) of 100 mg AS orodispersible tablets were prepared using 3 different superdisintegrants namely, sodium Starch glycolate, crosscarmellose sodium and crosspovidone at 3 different concentrations (3, 5 and 8%). Mannitol was used as sugar based excipient and bulking agent. Avicel 102 was used as a binder **(Rowe et al, 2003)**. Sucralose was used a sweetening agent to mask bitter taste of AS. Magnesium stearate was used as lubricant.

All the ingredients were passed through mesh no. 230 separately and collected. Atropine sulfate, sucralose and Avicel 102 were mixed uniformly and gently in plastic bags to get a uniform mixture by using geometric dilution method. Superdisintegrant was added by intragranular and extragranular method. Half of superdisintegrant quantity was added to previous mixture. Another half of superdisintegrant quantity was added to mannitol. Then, two mixtures were blended together geometrically in plastic bags till final homogenous mixture attained. Finally, magnesium stearate was applied. The blend was tested for preformulation studies as it previously mentioned. The different blend

formulae were compressed using Tablet Press Machine, a single punch tablet machine (Korsch XP1, Germany) on a flat punch with a diameter (6 mm) into 500 tablets. The force of compression was kept constant during the whole experiment.

Table 1: Composition of atropine sulfate ODTs

Composition	F1	F2	F3	F4	F5	F6	F7	F8	F9
Atropine sulfate	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg
Sodium starch glycolate	3 mg	5 mg	8 mg	------	------	------	------	------	------
Crosscarmellose	------	------	------	3 mg	5 mg	8 mg	------	------	------
Crosspovidone	------	------	------	------	------	------	3 mg	5 mg	8 mg
Avicel 102	13.5	13.5	13.5	13.5	13.5	13.5	13.5	13.5	13.5
Mannitol	79.5	77.5	74.5	79.5	77.5	74.5	79.5	77.5	74.5
Sucralose	1 mg	1 mg	1 mg	1 mg	1 mg	1 mg	1 mg	1 mg	1 mg
Mg.strearate	1 mg	1 mg	1 mg	1 mg	1 mg	1 mg	1 mg	1 mg	1 mg
Total weight	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg

Quality control of prepared tablets

A. Weight variation test

Twenty tablets were selected randomly and average weight was calculated. Standard deviation was reported. According to European pharmacopeia no more than two of the individual weights may deviate from the average weight by more than 5% (percent deviation), and none deviate by more than twice that percentage **(EP, 2019).**

B. Thickness test

Ten tablets were randomly taken and the thickness was measured using a Vernier caliper. The tablet thickness should be controlled within a ± 5% variation of a standard value. It is expressed in millimeters (mm) **(Shukla et al., 2009).**

C. Hardness test

Hardness test is important which indicates the ability of tablets to withstand handling, shipping and storage. Tablet hardness was determined using Hardness Tester (Pharma Test, Hainburg, Germany) for 6 tablets with known weight and thickness of each batch; the average hardness and standard deviation were reported **(USP/NF., 2016c).**

D. Friability test

Sixty five tablets were weighed (initial weight) before putting them into the friabilator (Erweka, Germany) at 25 rpm and 4 min, and then tablets were de-dusted and weighed as final weight. The friability value should not exceed 1%. Friability percent was calculated as following:

$$\text{Friability \%} = \frac{\text{intial weight} - \text{final weight}}{\text{initial weight}} \times 100 \quad (6)$$ **(USP/NF., 2016b).**

E. Content uniformity determination

According to USP, the content uniformity test is performed for tablets that contain less than 25 mg or less than 25% of the active material and be within range between (90-110%) of the labeled amount. Ten tablets from each formulation were powdered. The powdered sample equivalent to 2 mg of drug was transferred to a 500 ml volumetric flask and dissolved in an amount of deionized water then the volume in flask was made up with suitable volume of deionized water. The flask was sonicated for 20 min then filtered using 0.45 µm syringe filter. Content was analyzed using HPLC method of analysis at λ max 210 nm. The percentage of drug present in the tablets was calculated according to **(USP/NF., 2016a).**

F. Wetting Time test

Six tablets were randomly selected and tested. One tablet was placed on double folded tissue paper in a dish having about 6ml of water. The time for complete wetting of the tablet is recorded as the wetting time. The time for complete wetting of the tablet was measured in seconds **(Basha et al., 2020)**.

G. In vitro disintegration test

Six tablets were taken and placed in the tubes of disintegration test apparatus (Erweka, Germany) which was filled with dispersion medium (deionized water) at a temperature of (37°C ± 2°C), the disintegration test apparatus operated until no residue of the tablet remained on screen. Stop watch was used to record time required for complete disintegration and standard deviation was calculated **(Aodah et al., 2015)**.

H. In vitro dissolution studies

It has been suggested that USP 2 paddle apparatus was the most suitable and common choice for orally disintegrating tablets, with a paddle speed of 50 rpm commonly used. Six tablets of each formula were tested. Dissolution was carried out in dissolution apparatus (A&E Lab China, 6 vessels) with dissolution medium 500 ml deionized water (HPLC grade) to simulate saliva fluid. The paddle was rotated at 50 rpm with medium temperature of 37±0.5 ºC **(Rachid et al., 2011)**. Five ml Samples were withdrawn at specified time intervals (0, 0.5, 1, 2 min). The withdrawn Samples were replaced with fresh media at each time interval. The samples were filtered using

0.45 µm syringe filter then adequately analyzed by HPLC method at the determined λ max 210 nm.

Accelerated stability study of the selected Atropine sulfate ODTs formulae

In the accelerated stability test according to ICH guidelines, tablets were packed in each high-density polyethylene (HDPE) bottle and sealed thermally, then placed in a humidity chamber (40 ± 2 °C and75 ± 5 % relative humidity), up to 3 months. At the end of each month, samples were withdrawn. Samples were evaluated for all physical parameters and drug content **(Raghavendra et al., 2010).**

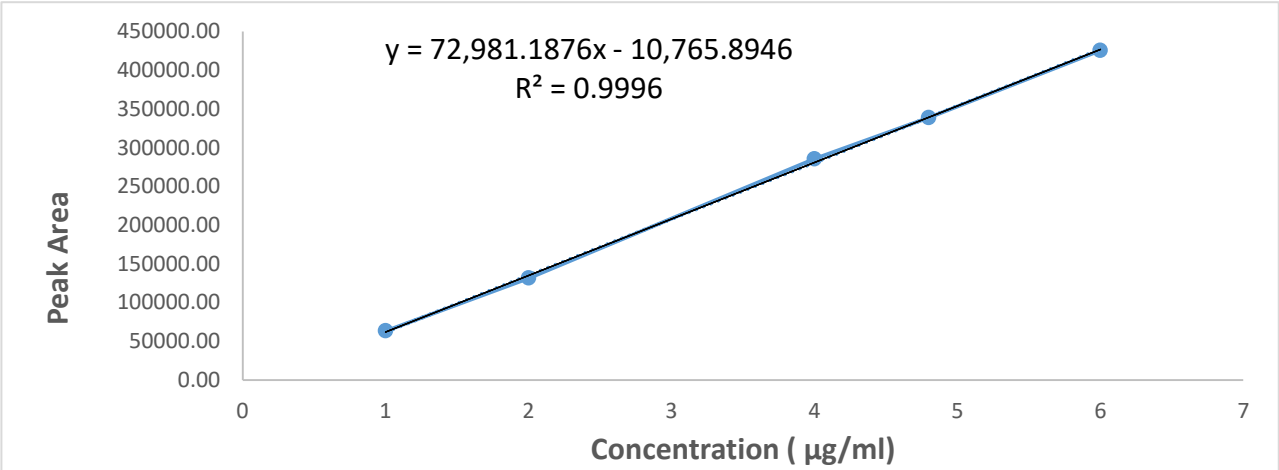
Results and Discussion

HPLC method for quantification of atropine sulfate

The method was validated according to norms of ICH guidelines for accuracy, precision, system selectivity and linearity. All results ranged within the accepted limits according to official limits. Small values of standard deviation indicated good suitability and reproducibility of method **(ICH, 1997).**

Construction of calibration curve

Five different concentration levels of 1-6 µg/ml were selected. It was found to give linear detector response in the concentration under study with correlation coefficient (R^2) of 0.9996 as in Figure 1. The limit of detection was found to be 0.16 µg



ml^{-1}, while limit of quantification was found to be 0.48 µg ml^{-1} .

Figure 1: Calibration curve of atropine sulfate at λmax 210 nm.

Compatibility studies

Differential scanning calorimetry (DSC)

The DSC of atropine sulfate was recorded as shown in Figure 3 which it showed endothermic peak at corresponding melting point at 190-194^{0}C **(Budavari , 1996).** The DSC thermograms of drug and different excipients as physical mixtures confirmed as shown in (Figure 2-5). It showed there were no new peaks found and endothermic to exothermic change did not occur. Hence, it was confirmed that there was no interaction between drug and excipients.

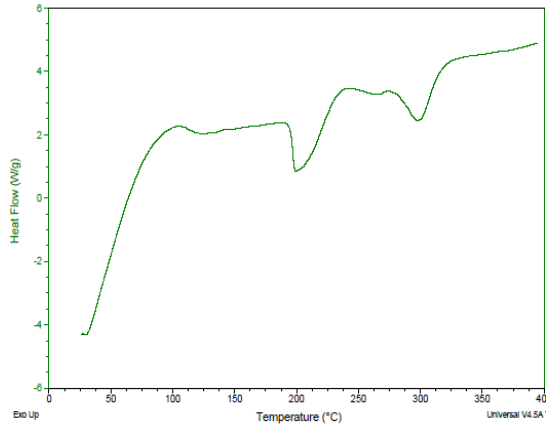


Figure 2: DSC thermogram of atropine sulfate and physical mixture of crosscarmellose based formula

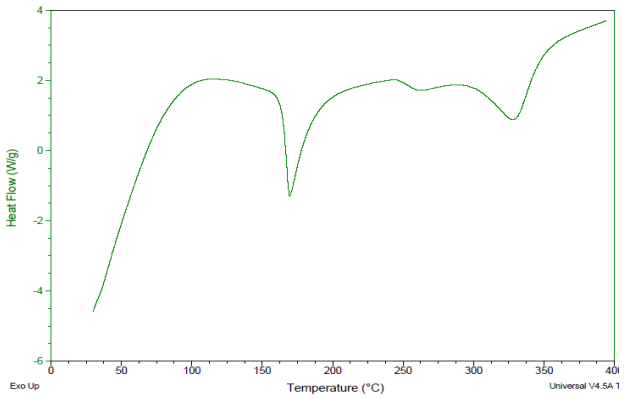


Figure 3: DSC thermogram of atropine sulfate

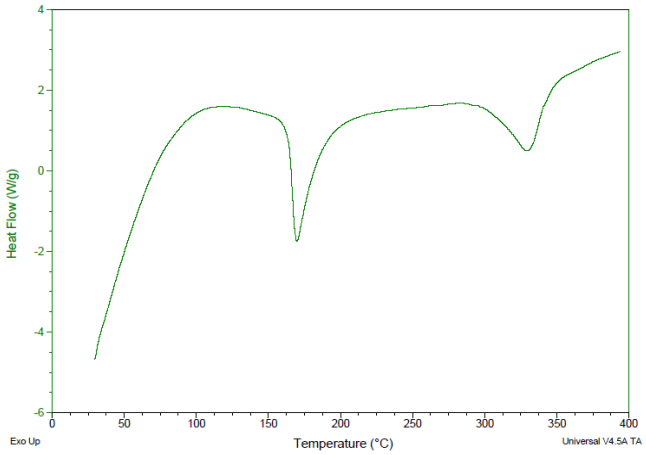


Figure 5: DSC thermogram of atropine sulfate and physical mixture of sodium starch glycolate based formula

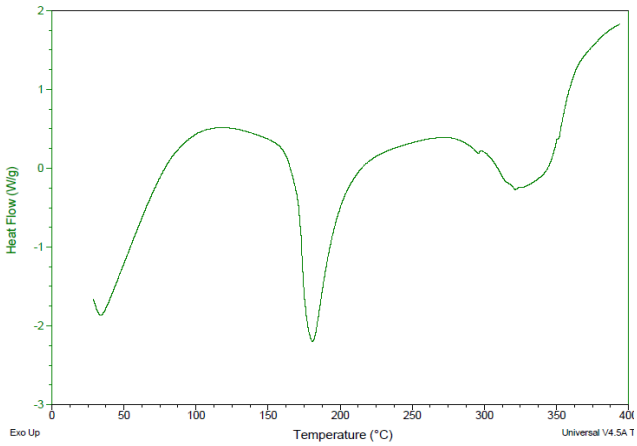


Figure 4: DSC thermogram of atropine sulfate and physical mixture of crosspovidone based formula

Fourier-Transform Infrared Spectroscopy (FTIR)

IR spectra of atropine sulfate monohydrate indicated characteristic peaks belonging to major functional groups which were similar to standard peaks. As shown in (Figure 6) the principal peaks were observed at 619.27, 669.18, 1165.55, 1478.2, 1581, 1727.54, 2874.69, 2963.91, and 3376. cm^{-1}. Assignments for the major IR absorption bands were provided in Table 2**.**

IR spectra of atropine sulfate with all the excipients (see in Figure 7-9) under test in mixtures showed the same characteristic bands of the drug in the same regions and ranges, indicating no sign of chemical interaction between the drug and excipients.

Table 2: Major IR absorption bands for atropine sulfate with physical mixtures

Ser#	Functional Group	IR Range (cm^{-1})	**IR Observed Peaks**			
			Atropine sulfate	AS& physical mixture(SSG)	AS& physical mixture(CCS)	AS& physical mixture(CP)
1	O-H bending (out of plane)	590-630	619.27	618.49	626.75	621.37
2	C=C (bending)	665-730	669.18	666.83	666.57	669.07
3	C-O (stretching)	1163-1210	1165.55	1165.81	1168.14	1164.74
4	C=C (Aromatic stretching)	1400-1600	1478.2	1467.02	1463.62	1467.06
5	N-H (bending)	1570-1650	1581	1577.96	1580.33	1577
6	C=O (stretching)	1715-1730	1727.54	1726.9	1724.15	1726.9
7	CH2 (stretching)	2850-3000	2874.69	2850.3	2850.56	2850
8	CH3 (stretching)	2850-3000	2963.91	2918.17	2917.31	2918.2
9	O-H (stretching)	3200-3500	3376.83	3376.24	3400.04	3329.33

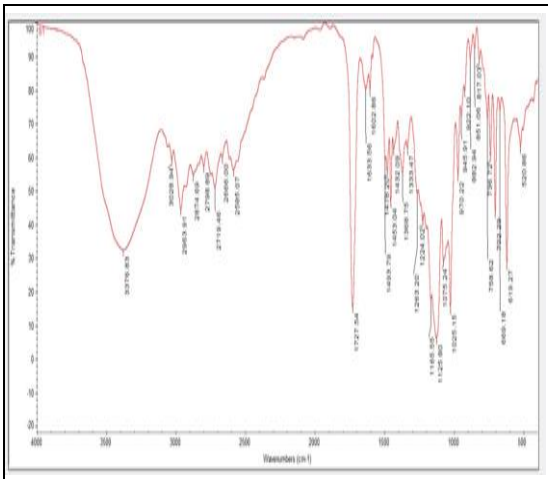


Figure 6: FTIR spectra of atropine sulfate

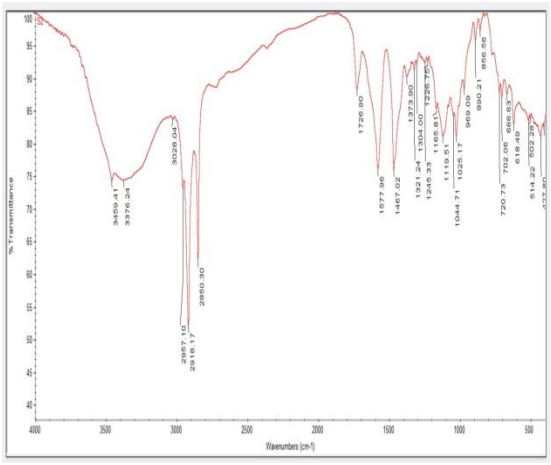


Figure 7: FTIR spectra of atropine sulfate with sodium starch glycolate based formula.

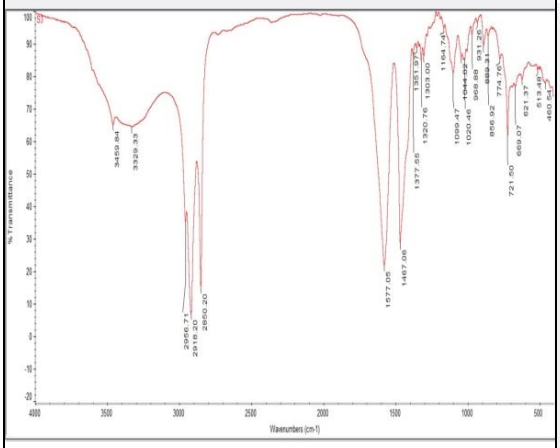


Figure 8: FTIR spectra of atropine sulfate with crosspovidone based formula.

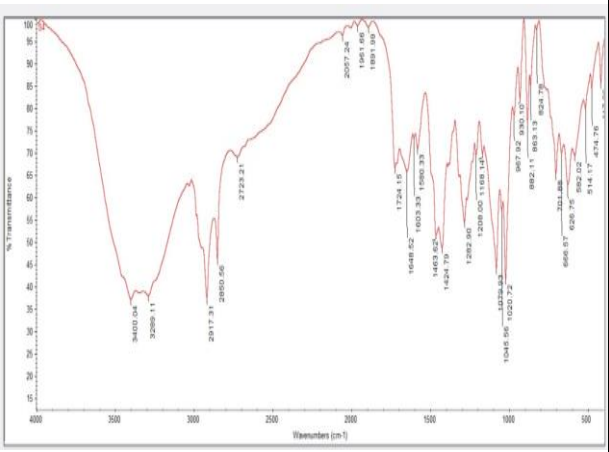


Figure 9: FTIR spectra of atropine sulfate with crosscarmellose sodium based formula

Flowability studies of blended powder

Precompression studies included the evaluation of tablet powder blend for the physical properties like angle of repose, tapped density, bulk density, Carr's index, Hausner's ratio. Their results were summarized in Table 3.

Table 3: Evaluation of powder blend for formulations (F1-F9)

Formulations	Bulk density (g/ml)	Tapped density (g/ml)	Angle of repose (^{0})		Carr s index (%)		Hausner's ratio		Total rank order	Rank order score
			Result	Rank order	Result	Rank order	Result	Rank order		
F1	0.481± 0.03	0.621± 0.012	32.41± 0.54	8	22.544± 0.34	8	1.291± 0.25	8	24	8
F2	0.461± 0.07	0.5688±0 .021	28.8±0.8 7	5	18.952± 0.55	5	1.233±0 .054	5	15	5
F3	0.481± 0.015	0.599±0. 14	31.4±0.8 6	7	19.699± 0.85	6	1.245±0 .03	6	19	6
F4	0.479± 0.05	0.611±0. 015	29.3±0.6 8	6	21.603± 0.34	7	1.27±0. 4	7	20	7
F5	0.473± 0.01	0.575±0. 018	27.299±0 .94	3	17.7±0. 58	4	1.215±0 .038	3	10	4
F6	0.476± 0.033	0.578±0. 012	27.29±0. 34	3	17.6±0. 63	3	1.214±0 .098	2	8	3
F7	0.491± 0.01	0.642±0. 05	34.12±0. 58	9	23.5±0. 67	9	1.305±0 .22	9	27	9
F8	0.473± 0.001	0.559±0. 013	23.85±0. 67	2	15.77±0 .41	1	1.215±0 .23	3	6	2
F9	0.48±0 .02	0.571±0. 02	21.0169± 0.39	1	15.9±0. 12	2	1.189±0 .03	1	4	1

The above results predicted that, the Carr's index was in the range of (15.77±0.41-22.544± 0.34) which was considered as good compression property. Angle of repose less than 35° gave very good flow property to the powder blend. Hausner's ratio Values ranged between (1.189±0.03-1.305±0.22) which it gave good flow property. Similarly, the bulk density and tapped density value was found to be less than one. Hence had good flow property so, all these results indicated that, the powder blend possess satisfactory flow and compressibility properties.

Quality control of prepared tablets

All ODTs were evaluated for various physical parameters like weight variation, hardness, friability, thickness and content uniformity of prepared formulae tablets using different combinations of functional excipients as it was shown in Table 4. Weight

variation in all formulae ranged from 98.87±2.8 to 103.23±1.84 which showed accepted results and allowed limit of deviation i.e. 5% of the standard value according EP range **(EP, 2019).** The average thickness for all formulations was found to be in range from 3.54± 0.03 to 3.68± 0.022 and small values of standard deviation showed good results of test so the tablets of all formulations showed uniform thickness. All prepared ODTs showed hardness values ranged from 24.71±2.4 N to 47.1±1.75 N and this range is optimum for ODTs **(El-Shafei et al. 1998).** The average percentage friability for all the formulations was between 0.18±0.01% and 0.87± 0.05% which was found to be within the limit as per USP (maximum 1%). The percentage drug content of all formulations was found in the range of (95.1±4.6%w/w - 105.3±4.3%w/w), which was all within the acceptable limits of official standards (90-110%) **(USP/NF., 2016a).**

Table 4 : Post compression parameter results

Formulations	Weight variation (mg) ± SD		Thickness (mm) ± SD		Hardness (N) ± SD		Friability (%)		Content Uniformity %± SD		Total rank order	Rank order score
	Result	Rank order	Result	Rank order	Result	Rank order	Result	Rank order	Result	Rank order		
F1	100.28 ±2.4	2	3.54± 0.03	1	24.71 ±2.4	1	0.87± 0.05	9	99.7± 4.5	1	14	2
F2	102.21 ±2.7	8	3.66± 0.02	6	41.8± 3.1	8	0.21± 0.012	3	105.3 ±4.3	9	34	8
F3	101.68 ±3.14	6	3.68± 0.022	9	25.38 ±3.7	2	0.65± 0.024	8	95.1± 4.6	8	33	7
F4	102.12 ±1.78	7	3.66± 0.03	6	28.1± 2.5	4	0.52± 0.015	6	98.6± 3.8	4	27	6
F5	100.41 ±4.8	3	3.648 ± 0.018	5	41.1± 2.9	6	0.23± 0.032	4	100.9 ±3.0	3	21	3
F6	99.33± 2.5	4	3.652 ± 0.017	4	41.5± 2.4	7	0.26± 0.045	5	98.05 ±5.3	5	25	4
F7	103.23 ±1.84	9	3.67± 0.02	8	27.6± 2.2	3	0.61± 0.04	7	95.9± 3.6	7	34	8
F8	98.87± 2.8	5	3.62± 0.01	3	47.1± 1.75	9	0.19± 0.037	2	97.5± 3.4	6	25	4
F9	100.06 ±4	1	3.585 ± 0.01	2	39.6± 2.8	5	0.18± 0.01	1	100.7 5±2.9	2	11	1

By comparing different types of co-processed excipients-based formulae (F1-F9) as in Table 5, we revealed that the shortest disintegration time (DT) was observed in

crosspovidone based formulae F8 and F9 (10.3±0.9 and 11.3±1.4 s) respectively, shorter DT of crosscarmellose sodium based formulae F4, F5 and F6 (24±2.1, 12.8±1.7 and 12.6±1.7 s) respectively and more time sodium starch glycolate based formulae F1,F2 and F3 (58±2.1, 37.6±10.4, 32±1.2 s), respectively as in Table 5 .

Based on previous results, it was found that by increasing superdisintegrant concentration, disintegration time decreased. Results of crosspovidone based formulae showed shortest formulae due to the rapid uptake of water from the medium, swelling and burst effect **(Kulkarni SV et al., 2011).**

From the results of wetting time (WT) shown in (Table 5), it was found that results ranged between 24.8±3.7 and 158.8±2 s. By comparing different types of co-processed excipients-based formulae, it revealed that crosspovidone based ODTs F9 (24.8±3.7 s) has the shortest wetting since it was assigned to its rapid water absorbing nature involving both capillary and swelling mechanisms. As well as the presence of Avicel 102 that enhanced greatly its wetting time **(Brniak et al. 2013).**

Table 5 : Rapidly disintegrating properties of all formulations

Formulations	Disintegration time (sec ± SD)		Wetting time (sec ± SD)		Total rank order	Rank order score
	Result	Rank order	Result	Rank order		
F1	58±2.1	8	32.1±4.7	6	14	7
F2	37.6±10.4	7	62.16±3.6	8	15	8
F3	32±1.2	6	51.2±4.1	7	13	6
F4	24±2.1	5	29.8±2.6	4	9	4
F5	12.8±1.7	4	30.3±1.7	5	9	4
F6	12.6±1.7	3	27.7±2.3	2	5	3
F7	72±1.5	9	158.8±2.6	9	18	9
F8	10.3±0.9	1	29.4±1.2	3	4	2
F9	11.3±1.4	2	24.8±3.7	1	3	1

In vitro dissolution studies

In-vitro dissolution studies were done at 37 ±0.5°C using medium of deionized water. The data presented that the results of dissolution were in accordance with the obtained results of the wetting time and disintegration time. Formulae containing crosspovidone F8 and F9 (92.92, 102.22 %) respectively exhibited more than 90% dissolved of the drug as well as Formulae containing crosscarmellose sodium F4, F5 and F6 (92.45, 90.97 and 96.09 %) respectively .On the other hand, sodium starch glycolate based formulae F1, F2 and F3(80.5, 83.10, 88.45 %) respectively exhibited less than 90% of drug released.

Also, dissolution of crosspovidone (3%) based formula (F7) was notably retarded and showed the lowest drug dissolution. High dissolution rate of crosspovidone based formula (F8 and F9) may be as crosspovidone acts via different mechanisms including the swelling, and wicking followed by secondary swelling, high hydration capacity, and low bulk density.

Crospovidone also swells without gelling, a property that is advantageous for developing orally disintegration tablets and where gelling can delay the dissolution process. When compaction force is applied, the polymer deforms. Upon contact with water, it absorbs water via capillary action and regains its normal structure releasing an amount of energy capable to break the tablet. The particle size of crosspovidone strongly affects the disintegration process, and larger particles provide a faster disintegration. As size increases, the intra-particular porosity increases, leading to larger water uptake and faster disintegration (**Barabas and Adeyeye, 1996).**

Retardation of dissolution as in F1, F2, F3 and F7 could be attributed or possibly as a result of relatively prolonged disintegration time, as mentioned before, due to formation of wet sticky mass after the contact of a tablet with water **(Brniak et al. 2013)**. Dissolution profile of different AS ODTs formulae was represented in **Table 6**.

Table 6: In-vitro dissolution profile of different atropine sulfate ODTs formulas (F1-F9).

Time (sec)		**Percent drug release%**								
		F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	**Result**	0	0	0	0	0	0	0	0	0
30	**Result**	18.02±3.5	25.2±2.8	24.1±2.4	28.12±2.11	30.9±5.1	30.4±5	11.1±2.1	32±5.6	37.4±0.5
	RO	8	6	7	5	3	4	9	2	1
60	**Result**	48.47±1.5	56.2±3.5	60.1±3.1	75.11±1.2	78.8±4.2	63.6±5.7	30.1±.9	53.7±8.3	97±5.4
	RO	8	6	5	3	2	4	9	7	1
120	**Result**	80.5±4.3	83.1±1.18	88.45±0.9	92.2±3.1	90.9±7.4	96±5.19	73.11±1.1	92.9±5.9	102.2±2.6
	RO	8	7	6	4	5	2	9	3	1
Total rank order		24	19	18	12	10	10	27	12	3
Rank order score		8	7	6	4	2	2	9	4	1

By comparing different types of co-processed excipients-based formulae at the same drug to excipient ratio, crosspovidone (8%) based formulae (F9) showed the best dissolution which is (102.22%) within 2 minutes (**Figure 10**). Formula F9 had

superdisintegrant Crospovidone in the concentration of 8% showed highest percent drug release 102.2%, after 2min.

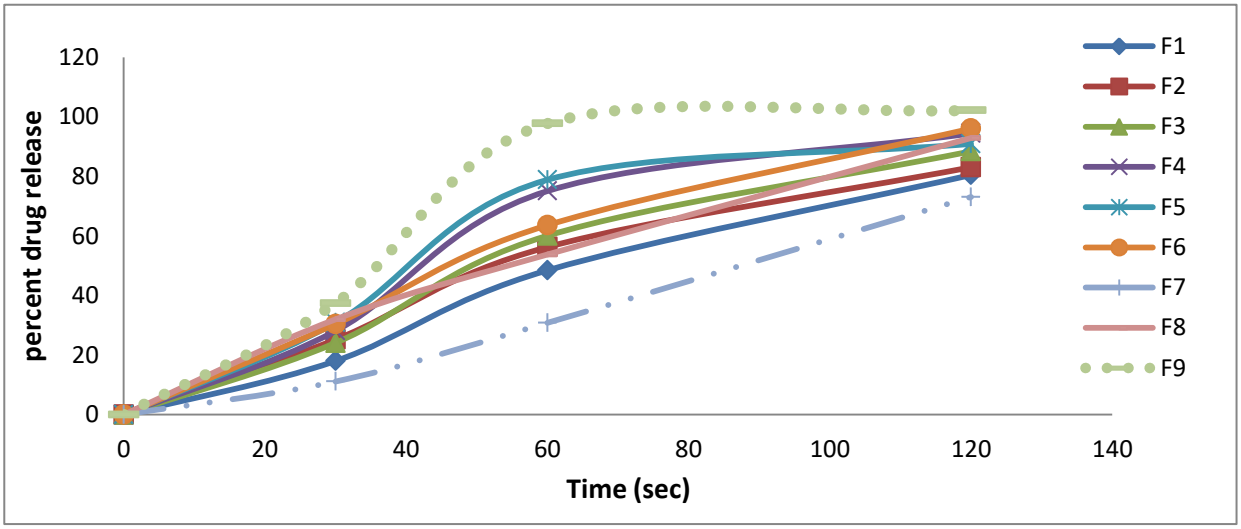


Figure 10: Dissolution profile of Atropine sulfate ODTs formula

Rank order for all formulae

All formulae prepared were subjected for rank order for all flowability properties, post compression parameters, rapid disintegrating properties and Invitro dissolution studies.
Based on the results of the rank order, it was found that crosspovidone based formula (8%), F9 obtained the best results in all the tests conducted on all formulations as in **Table 7** and it can be subjected for further stability studies.

Table 7: rank order for all formulae

F.NO	Flowability properties	Post compression parameters	DT& WT	Invitro dissolution study	Total rank order	Rank order score
F1	24	14	14	24	76	6
F2	15	34	15	19	83	7
F3	19	33	13	18	83	7
F4	20	27	9	12	68	5
F5	10	21	9	10	50	4
F6	8	25	5	10	48	3
F7	27	34	18	27	106	9
F8	6	25	4	12	47	2
F9	4	11	3	3	21	1

Accelerated stability studies

The selected formula F9 showed no significant change in all physical parameters thus successfully passed the accelerated stability study which was conducted for 90 days (Table 8 & Figure 11). Thus the selected formula passed the stability test since none of the examined parameters were outside the respective acceptance limits.

Table 8: Evaluation of physical parameters of selected Atropine sulfate ODT formula (F9) at 40±2 ºC and 75±5 % relative humidity.

Time (day)	parameters					
	Appearance	Weight	Hardness	Friability	Disintegration time	Assay
0	white	99±2	43.2	0.23	12.1±0.78	102.74
30	Same as 0 day	99.53±2.2	42.6±3.7	0.24	13.36±0.6	101.11
60	Same as 0 day	99.8±1.8	42.6±4	0.31	12.3±0.9	100.91
90	Same as 0 day	99.97±1.29	30.4±3	0.63	9.66±.86	96.65

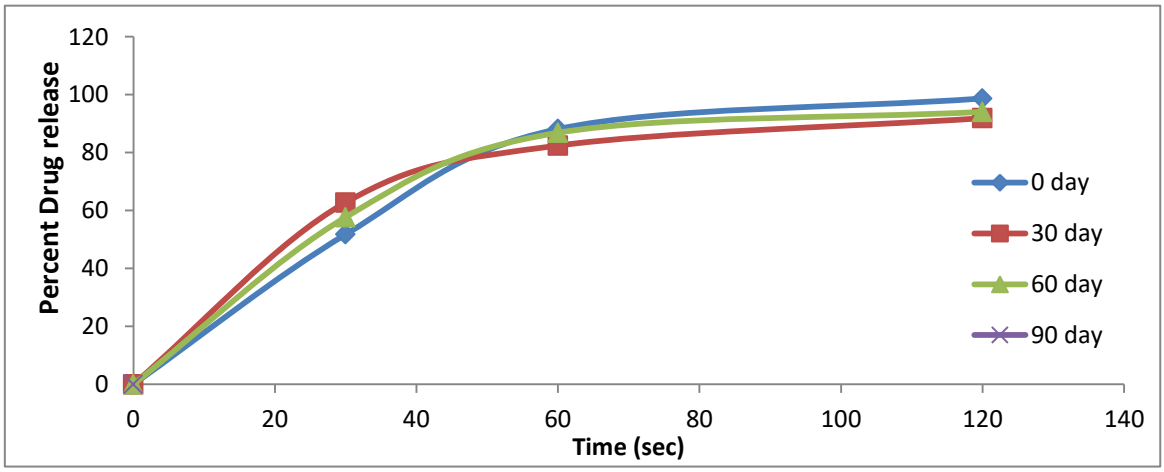


Figure 11: In-vitro dissolution profile of selected Atropine sulfate ODT formula (F9) at 40±2 ºC and 75±5 % relative humidity.

Conclusion

Based on results in this scientific paper work, the selected ODT formula (F9) showed best results in all powder flow properties studies of the blend as bulk density, tapped density, compressibility index, Hausner's ratio, and angle of repose and post-compression parameters such as thickness, weight variation, hardness, friability, drug content, disintegration time, wetting time, and in vitro dissolution studies.it showed good stability under accelerated condition. At the end of this investigation it can be concluded that orodispersible tablet of atropine sulfate was successfully prepared by

direct compression technique using crosspovidone (8%) as superdisintegrant and the objectives of this study can offer an alternative non-invasive and portable dosage form for treatment of various emergency health conditions as treatment of organophosphate (OP) toxicity.

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تحضير وتوصيف أقراص كبريتات الأتروبين القابلة للتشتت بالفم

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يعتبر اعطاء الدواء عن طريق الفم هو الطريق الأكثر قبولا على نطاق واسع. توفر البيئة الفريدة لتجويف الفم إمكانات كموقع جيد لتوصيل الأدوية. كان الهدف من الدراسة الحالية هو صياغة وتقييم اقراص قابلة للتشتت من كبريتات الأتروبين كشكل جرعات بديل للحقن ومحمول لعلاج الحالات المرضية الطارئة المختلفة كعلاج للتسمم بالفوسفات العضوي .الحقن التلقائي هو الشكل الوحيد الذي يتم تناوله ذاتيًا والمتوفر كترياق للاستخدام في حالات الطوارئ خارج المستشفى، ولكنه يرتبط بالعديد من القيود والعيوب. فى هذه الدراسة تم تحضير تسع تركيبات باستخدام مواد مفككة فائقة مختلفة، وهي غليكولات نشا الصوديوم، والكروسبوفيدون، وكروسكرميلوز الصوديوم بتركيزات مختلفة (٣، ٥، و٨%). تم إجراء دراسات توافق الدواء والسواغات بواسطة اجراء التحليل الطيفى باستخدام الاشعة تحت الحمراء وقياس المسح التفاضلى. تم تقييم المزيج النهائي من الدواء والسواغات لخصائص تدفق خليط البودرة مثل الكثافة الظاهرية، والكثافة المستغلة، ومؤشر الانضغاط، ونسبة هاوزنر، وزاوية السكون. تم تقييم الاقراص المحضرة للصياغات التسعة من خلال اختبارات ما بعد الضغط مثل سمك القرص، اختلاف الوزن للاقراص ، صلابة القرص، هشاشة القرص، نسبة الدواء، زمن التفكك، زمن التبلل، ودراسات معدل انطلاق الدواء في المعمل، وقد وجد أن الصياغة رقم ٩حققت أفضل النتائج حيث كان زمن التفكك قصير (١١ ثانية) وزمن التبلل (٢٤.٨ ثانية). مع إطلاق الدواء بنسبة ١٠٢.٢٢% بعد دقيقتين، تم إخضاع الصياغة رقم ٩ لدراسة الثبات الحرارى لمدة ٣ أشهر، والتي أظهرت عدم وجود تغييرات ملحوظة في جميع الخواص الفيزيائية والكيميائية.

الكلمات المفتاحية: أقراص قابلة للتشتت بالفم ، كبريتات الأتروبين ، الفوسفات العضوي، كروسبوفيدون، جليكولات نشا الصوديوم، كروس كارميلوز الصوديوم، والضغط المباشر.