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FORMULATION AND EVALUATION OF DROTAVERINE ORALLY DISINTEGRATING TABLETS

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ABSTRACT

The pharmaceutical industry widely acknowledges oral drug delivery as the most preferred method for administering medications due to its numerous advantages, including safety, convenience, cost-effectiveness, and high patient compliance. The study aimed to develop Orally disintegrating tablets of Drotaverine hydrochloride, evaluate the effects of superdisintegrants on disintegration time, drug release, and overall efficacy, with the goal of enhancing bioavailability and achieving rapid onset of action. The study involved evaluating the color, odor, and taste of Drotaverine hydrochloride and the formulated tablets. The general appearance, including color, odor, and taste, of the tablets was examined. The physical properties such as diameter, hardness, thickness, and weight variation of the tablets were measured. The wetting time and disintegration time of the tablets were determined. *In-vitro* dissolution studies were conducted in phosphate buffer and 0.1 N HCl, and the drug release percentages were measured.

The organoleptic properties of Drotaverine hydrochloride were found to be pale yellow color, no characteristic odor, and a bitter taste. Eleven formulations were prepared using (Beta-cyclodextrin, Klucel, mannitol, microcrystalline cellulose, aerosil 200, croscarmellose

sodium, sodium starch glycolate, stearic acid, magnesium stearate, aspartame, sucralose, menthol and thymol). After evaluation, the results of disintegration time of F10 formulation indicated that the tablets dispersed rapidly in mouth was found to be 8 seconds, while the drug release was found to be 86.7 % within 5 minutes in 0.1 N HCl. The addition of croscarmellose sodium as a superdisintegrant in the formulation enhanced the dissolution rate of Drotaverine, leading to rapid drug release and absorption. It was concluded that F10 is the best formulation of Drotaverine hydrochloride ODTs in order to increase onset of action and bioavailability of drug. The study demonstrates the potential of superdisintegrant methods to improve the dissolution rate of Drotaverine and enhance its therapeutic effects.

KEYWORDS: Drotaverine hydrochloride, Drug delivery system, Orally disintegrating tablets, Formulation.

INTRODUCTION

Oral drug delivery is widely recognized as the gold standard in the pharmaceutical industry, providing a safe, convenient, and cost-effective method of administering drugs with high patient compliance. Tablets and capsules are the preferred dosage forms for oral delivery, but they have limitations such as the risk of choking and discomfort, especially among geriatric and pediatric patients. To overcome these challenges, Orally disintegrating tablets (ODTs) have been developed, incorporating innovative technologies to meet diverse pharmaceutical and patient needs. These tablets, also known as oro dispersible, rapid-dissolving, mouth-dissolving, or rapid disintegrating tablets, disperse quickly in the mouth before swallowing.[1,5]

Pharmacopeias and regulatory agencies have provided definitions for Orodispersible tablets and Orally disintegrating tablets. Orodispersible tablets are uncoated tablets that disperse within 180 seconds during disintegration tests. Orally disintegrating tablets, on the other hand, are solid dosage forms designed to rapidly disintegrate in the mouth, ensuring dispersion before swallowing. They are mainly used for gastrointestinal delivery and absorption of the active ingredient. The FDA recommends that Orally disintegrating tablets should disintegrate rapidly in the mouth, with an *in-vitro* disintegration time of approximately less than or equal to 30 seconds, as per the United States Pharmacopeia (USP) disintegration test method or an alternative method.[6-20]

The presence of superdisintegrants in Orodispersible tablets facilitates rapid dissolution, leading to fast drug absorption and onset of action. This direct absorption from the mouth enhances drug bioavailability and bypasses first-pass metabolism. The advantages of this drug delivery method include quick onset of action, improved bioavailability, enhanced patient compliance, and the ability to accommodate high drug loads. Recent advancements have introduced various techniques for formulating Orodispersible tablets, such as direct compression, molding, extrusion, sublimation, spray-drying, cotton candy, lyophilization, thin film, and nanoionization.

Characterization techniques focus on factors like mechanical strength, drug stability, disintegration time, dissolution rate, taste, absorption rate, and drug bioavailability.[21,43]

Drotaverine hydrochloride is an analogue of papaverine. It is phosphodiesterase IV enzyme inhibitor and acts as an antispasmodic agent. The absorption of Drotaverine is not completely absorbed following oral administration and its bioavailability is highly variable. [6-20]

The main objective of the study was to develop Orally disintegrating tablets (ODTs) of Drotaverine hydrochloride and investigate the impact of superdisintegrants, specifically sodium starch glycolate and croscarmellose sodium, on the disintegration time, drug release, and overall effectiveness of the tablets. The study aimed to improve the bioavailability and achieve a quick onset of action for Drotaverine hydrochloride.

MATERIALS AND METHODS

Drotaverine hydrochloride, Croscarmellose Sodium, Beta-Cyclodextrin, Sodium Starch Glycolate, Mannitol, Aerosil200, Stearic Acid, Magnesium Stearate, Microcrystalline Cellulose, Hydroxypropyl Cellulose (Klucel), Aspartame, Sucralose, Menthol and Thymol were gift from (Global Pharmaceutical Industry Company-Yemen).

Preparation of Powder Blends for Compression of Drotaverine Formulations

Orally disintegrating tablets containing selected solid dispersion were prepared by direct compression method using single punch tablet machine to produce convex faced tablets part of them weighing 200mg. 150 tablets were prepared for each batch. The formulations were developed by using Superdisintegrants. The superdisintegrants (Croscarmellose sodium and sodium starch glycolate) in varying concentration (2- 10%) were used to develop the tablets. All the ingredients were shown in Table 1 were passed through sieve no.18 except

magnesium stearate passed through sieve no 35 and were co-grounded in a glass pestle motor. The mixed blend of excipients was compressed using rotary tablet compression machine of punch size 6.25mm (chamber diameter 7mm) to produce convex faced tablets.

Mixing and Compression Processes of Drotaverine Formulations

Mixing was done by using geometric mixing, in where all excipients accurately weighed then all of them except silicon dioxide, magnesium stearate, were blended with specified quantity of Drotaverine for 15minutes, whereas the other excipients were blended for 5 minutes and added to the former excipients. Then all formulae were passed through sieve # 18 for particle size uniformity. This method of ordering mixing of excipients with Drotaverine in first sex formulae. Then each mixture has compressed directly into tablets using rotary tablet compression machine of punch size 6.25mm (7mm) to prepare tablets each weighing 200mg. Compatibility studies were carried out between Drotaverine and commonly used tablet excipients in the preformulation stage.

Table 1: Composition of Drotaverine Formulations ODTs.

Ingredients	Quantity Per Tablet(mg)										
	Formulation Code										
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Drotaverine hydrochloride	40	40	40	40	40	40	40	40	40	40	40
Beta-Cyclodextrin	---	---	---	---	40	40	40	60	---	60	40
Mannitol	146.40	146.40	126.40	144.244	102.844	104.844	43.797	64.50	69.90	49.50	62
Microcrystalline Cellulose	---	---	---	---	---	---	69	25	50	25	30
Croscarmellose Sodium	8	8	8	8	8	8	2	8	8	8	5
Sodium Starch Glycolate	---	---	---	2	4	2	3	---	---	---	---
(Klucel) Hydroxypropyl Cellulose	2	2	2	2	2	2	---	---	---	---	---
Aerosil 200	0.4	0.4	0.4	0.4	0.4	0.4	0.5	0.5	0.5	0.5	0.5
Stearic Acid	---	---	20	---	---	---	---	---	29.6	15	19.5
Magnesium Stearate	1	1	1	0.75	0.75	0.75	0.7	1	1	1	1
Aspartame	1	1	1	1	1	1	---	---	---	---	1
Sucralose	---	---	---	1	1	1	1	1	1	1	1
Menthol	0.6	0.6	0.6	0.006	0.003	0.003	0.003	---	---	---	---
Thymol	0.6	0.6	0.6	0.6	0.003	0.003	---	---	---	---	---
Total	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**

Evaluation of Drotaverine ODTs [1-20]

The first step seven formulae were prepared to mask the taste by adding the sweetening agents in different concentrations. The second step was to get other properties of evaluation such as dissolution, disintegration, diameter, hardness, and thickness of the tablets.

POST Compression Parameters

The compressed tablets were evaluated for the following parameters.

General appearance

The physical appearance of drug was examined by various organoleptic properties. The general appearance of tablets, its visual identity and overall 'elegance' is essential for consumer acceptance. The control of general appearance involves measurement of attributes such as a tablet's size, shape, color presences or absence of odor, taste.

Weight Variation

The weight of tablet being made is routinely measured to ensure that a tablet contains the proper amount of drug. As per IP/BP the weight variation test is run by weighing 20 tablets individually, calculating the average weight and comparing the individual tablet weights to the average. The weight variation test would be satisfactory method of determining the drug content uniformity. Twenty tablets randomly were taken from each batch and weighted individually, calculating the average weight, and comparing the individual tablet weights to the average.

Diameter Test

The diameter is one of tests which used for determination of the tablets size, it is done by taking five tablets from each batch randomly. Diameter may obtain by using suitable micrometer.

Thickness Test

The thickness was determined for ten pre-weighed tablets of each batch using a Vernier, and the average thickness were reported. The thickness was denoted in millimeter.

Hardness Test

The hardness test is done to determine whether the tablets will be able to withstand the rigors of handling and transportation experienced in manufacturing plant, in the drug distribution systems and in the field at the hands of end sers (patients/consumers). Five tablets were

randomly selected from each batch and hardness is determined by using digital hardness tester. The mean values and standard deviation for each batch were calculated.

Wetting Time Test

The wetting test is the important step for disintegration process to take place. The wetting time of the tablets was measured using a simple procedure. Circular tissue paper of 10cm diameter were placed in a petri dish with a 10cm diameter. 10ml of distilled water containing a yellow water- soluble dye (sunset dye), were poured into the tissue paper placed in the petri dish. A tablet was placed carefully on the surface of the tissue paper. The time required for the solution to reach upper surface of the tablet was noted as the wetting time.

Disintegration Time Test

The disintegration test was carried out at 37C±2°C in 900 ml of distilled water. The disintegration time of tablets from each formulation were determined using disintegration test apparatus. One tablet was placed in each of the six tubes of the apparatus containing distilled water. One disk was added to each tube. The time taken in seconds for complete disintegration of the tablets with no palpable mass remaining in the apparatus was measured.

***In-vitro* Dissolution Studies of Drotaverine ODTs**

The Dissolution Parameters: Apparatus: dissolution Tester, Medium: 900 ml phosphate buffer at (PH 6.8), 900ml phosphate buffer in presence of SLS and in 0.1N HCl. RPM: 50., Temperature: 37°C ± 0.5°C Sampling interval: 3, 5, 10, 20 and 30minutes. Sample withdrawn: 5ml, Wavelength: 239.6 nm, Instrument: HPLC buffer at (pH 6.8): Dissolve 5.4g of NaOH and 40.83g of KH2PO4 into 6000ml of water. Adjust to a pH of 6.8 with 10M NaOH., Procedure: The in vitro dissolution studies of Drotaverine orally disintegrating tablets were performed using dissolution Tester. The volume of dissolution medium phosphate buffer at (pH 6.8) used was 900 ml and the temperature was maintained at 37°C±0.5°C. The speed of the basket was set at 50rpm. One tablet was placed in each vessel of dissolution apparatus. 5ml of sample from each jar was withdrawn at every 1minutes interval up to 30 minutes and same volume of phosphate buffer was replaced to each dissolution vessel, so that volume of dissolution medium was maintained to 900 ml. Then the sample was filtered and diluted with phosphate buffer and the amount of Drotaverine released from ODTs was determined by HPLC method. The same way for phosphate buffer in presence of SLS and 0.1 HCl medium.

HPLC Method: Chromatographic Conditions: Column: C18, 25 cm., Mobile phase: Buffer: Acetonitrile: Menthol (135: 730: 135). Adjust pH into 6.4 by G.A.A. Buffer: (10.88g Na-acetate + 30ml G.A.A) complete to 500ml by water. Flow rate: 1 ml/minute., Wavelength: 243.1 nm. Injection volume: 20µl. Preparation of Mobile Phase: Mix 135ml of buffer, 730ml of acetonitrile and 135ml of menthol, then filter. Preparation of Standard Solution: Weighed quantity equivalent 44mg of Drotaverine HCl standard to a 100ml volumetric flask dissolve with the mobile phase**.**

RESULTS AND DISCUSSION

Post Compression Parameters

The organoleptic properties of Drotaverine hydrochloride like color, odor and taste of the API were evaluated. The color of Drotaverine hydrochloride was found to be pale yellow, no characteristic odor was observed in the study and the taste was found to be bitter. Drotaverine HCl showed similar color, taste and odor as per IP specification as shown in Table 2.

Table 2: Organoleptic Properties of Drotaverine HCl (API).

Tests	Specification	Observation
Color	Pale yellow crystalline solid	**P**ale yellow crystalline solid
Odor	Almost odorless	Almost odorless
Taste	Bitter	Bitter

The general appearance of all formulations (F1 to F11) were examined and found to be as follows: Color: for formulations from F1 to F4 the color was pale yellow while for formulations from F7 to F11 the color results were given below in Table 3**,** Odor: all formulation did not have an odor, Taste: the taste was bitter for formulation F1 to F7 while the formulations from F8 to F11 the taste was good.

Table 3: Organoleptic Properties of Drotaverine Formulations.

Tests	Formulation Code				
	F7	F8	F9	F10	F11
Color	Pale Yellow	Yellow	Nearly White	Bright Yellow	Pale Yellow
Odor	Odorless	Odorless	Odorless	Odorless	Odorless
Taste	Bitter	Good	Good	Good	Good
Shape	Round	Round	Round	Round	Round

Table 4: Evaluation of Post Compression Parameters of Drotaverine Formulations ODTs.

Parameters	Formulation Code			
	F8	F9	F10	F11
Average Weight (mg)±S.D	206.6 ±10.33	201.7 ±10.09	202.6 ±10.63	205.7 ±10.18
Thickness Mean(mm)	4	4.5	4	4.5
Diameter (mm)	8.5	8.5	8.5	8.5
Hardness Kg/cm^2	69	23	20.6	26
Wetting Time (Sec)	33.8	97	18.9	31.3
In-vitro Disintegration Time (Sec)	307.7	30	8	30

As shown in Table 4 the diameter of the tablets was measured and were found to be 8.5 mm for all formulation. All the formulations possessed uniform diameter. The hardness of the tablets was measured and the values were found in the range between 20.6 to 69 Kg/cm^2. The prepared tablets possessed good mechanical strength with sufficient hardness except F10 it has lowest hardness. The thickness of the tablets was measured and were found in the range between 4mm to 4.5mm. All the formulations possessed uniform Thickness and in the accepted range.

All formulations of Drotaverine Orally disintegrating tablets passed the weight variation test since the values are within the acceptable variation limit of the tablet.

Wetting time of Drotaverine Orally disintegrating tablets were found to be in the range between 31.3 and 97 seconds. Formulation F10 prepared by using microcrystalline cellulose as superdisintegrant showed least wetting time (18.9 sec). Disintegration time of Drotaverine orally disintegrating tablets ranges between 8 to 307.7 seconds. The acceptable disintegration time limit as per I.P is NMT 30 seconds. Formulation F10 showed least disintegration time (8 sec) compared with all other formulations. From the above results, it was concluded that the formulation F10 showed better tableting properties when compared to the other formulations.

In-vitro Dissolution Studies

The percent of *in-vitro* drug release of Drotaverine ODTs were given in Table 5.

Table 5: Percentage of *In-vitro* Drug Release of Drotaverine Formulations ODTs in Phosphate Buffer (pH6.8).

Time (min)	Percentage Drug Release (%)			
	Formulation Code			
	F8	F9	F10	F11
3	79.8%	49.8%	50.4%	53.3%
5	80.0%	50.8%	58.1%	56.6%
10	83.4%	53.4%	60.5%	59.4%
30	83.9%	63.9%	66.4%	61.1%

Table 6: Percentage of *In-vitro* Drug Release of Drotaverine Formulations ODTs in Phosphate Buffer (pH6.8) Contain of *SLS*.

Time (min)	Percentage Drug Release (%)			
	Formulation Code			
	F8	F9	F10	F11
3	70.3%	52.4%	51.2%	52.2%
5	77.7%	55.3%	56.3%	54.1%
10	84.2%	58.7%	60.2%	58.7%
20	85.2%	62.1%	72.0%	62.1%
30	85.8%	66.8%	80.9%	64.3%

Table 7: Percentage of *In-vitro* Drug Release of Drotaverine Formulations ODTs in 0.1N HCl.

Time (min)	Percentage Drug Release (%)			
	Formulation Code			
	F8	F9	F10	F11
3	83.4%	71.3%	73.7%	33.9%
5	96.9%	85.5%	86.7%	44.1%
10	101.1%	90.6%	95.5%	45.7%
20	104.5%	96.5%	99.6%	46.7%
30	107.7%	100.5%	103.3%	56.2%

As shown in Tables 5, 6 and 7 Drotaverine release was studied in phosphate buffer pH (6.8), phosphate buffer pH (6.8) contain of SLS and in 0.1 N HCl for up to 30 minutes. The formulations F8, F9, F10 and F11were prepared along with excipients. The drug release of formulations F8, F9, F10 and F11 was found to be 80.0%, 50.8%, 58.1%% and 56.6% at 5 minutes in phosphate buffer. The drug release of formulations F8, F9 and F10, and F11 was found to be 77.7%, 55.3%, 56.3% and 54.1% at 5 minutes in phosphate buffer in the presence of SLS. While the drug release of formulations F8, F9, F10 and F11 was found to be 96.9%%, 85.5%, 86.7% and 44.1% at 5 minutes in 0.1 N HCl buffer which correlates the stomach medium. The acceptable *in-vitro* dissolution limit is not less than 80% of drug release at 5 minutes. Formulation F10 passed the *in-vitro* dissolution studies. F8 has the

higher dissolution rates were observed in prepared using croscarmellose sodium as superdisintegrant which may be due to rapid disintegration and fine dispersion of particles formed after disintegration and has maximum drug release.

From the above results and discussion, it was concluded that Drotaverine of Orally disintegrating tablets containing croscarmellose sodium i.e. F10 formulation can be taken as an optimized formulation of Orally disintegrating tablets for disintegration time was found to be 8 seconds. While F8 formulation for drug release was found to be 80.0 % and 96.9% release within 5 min in phosphate buffer pH (6.8) and 0.1 N HCl respectively. The study shows that the dissolution rate of Drotaverine can be enhanced through the great extent by addition of superdisintegrant methods. The rapid drug dissolution might be due to easy breakdown of the particles due to porous structure formation after superdisintegration addition method and rapid release of drugs into the dissolution medium.

CONCLUSION

Orally disintegrating tablets of Drotaverine hydrochloride were prepared by direct compression method using sodium starch glycolate and croscarmellose sodium as superdisintegrants. The tablets disintegrated rapidly in oral cavity and had acceptable results and in-vitro drug release from the tablets shows significantly improved drug dissolution. Hence it could be concluded that the superdisintegrant based Orally disintegrating tablets of Drotaverine would be quite effective in providing quick onset of action.

The absorption of Drotaverine is not completely absorbed following oral administration and its bioavailability is highly variable. Drotaverine was developed as Orally disintegrating tablets were prepared by direct compression using sodium starch glycolate and croscarmellose sodium as superdisintegrants. The other excipients added to enhance the organoleptic properties of tablets. The tablets were evaluated for weight variation, thickness, diameter, hardness, wetting time, disintegration time, and *in-vitro* dissolution study. The results of disintegration time of F10 formulation indicated that the tablets dispersed rapidly in mouth was found to be 8 seconds, while drug release was found to be 86.7% drug release within 5 minutes in 0.1 N HCl. It was concluded that F10 is the best formulation of Drotaverine hydrochloride ODTs in order to increase onset of action and bioavailability of drug.

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