

FORMULATION OF EXTENDED RELEASE ORPHENADRINE CITRATE TABLETS TO TREAT MUSCLE SPASM AND PAIN

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Submitted 23rd May 2020, Accepted 18th October 2020

ABSTRACT

Objective: Orphenadrine is an anticholinergic, antimuscarinic, centrally acting skeletal muscle relaxant. It presents in the form of citrate and HCl salts which are used in treatment of the symptoms of mild Parkinson's disease and also it is used as adjuvant with other drugs in the therapy. **Method:** Many trials were made to formulate orphenadrine citrate as tablet using wet granulation or direct compression technique in order to get a satisfactory formula through studying the effect of various factors such as binders, diluents and disintegrants types. The best formula was obtained by using poly vinyl pyrrolidone (PVP) as a binder also the results indicated that starch and mannitol gave acceptable physical properties to the tablets when they were used as diluents. At the same time, the results showed that avicel which was used as a disintegrant gave an acceptable disintegration and dissolution time in comparison with the reference tablet DISIPAL[®]. In addition, the selected formula was used to study the effect of method of incorporation of disintegrant on the physical properties of tablets. **Result:** It was found that the intragranular incorporation resulted in a shorter disintegration and dissolution times. The stability of orphenadrine citrate prepared tablets was also studied upon storage at 50°C, 60°C and 70°C for four months. **Conclusion:** The overall results of this study indicate that the drug can be prepared as tablets, which fit the requirements of British Pharmacopoeia since the prepared tablets gave satisfactory results.

Keywords: Extended release, Orphenadrine citrate, Tablet characterization.

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INTRODUCTION

The skeletal muscle relaxants are group of compounds used to relieve spasticity & abnormally high muscle tone [1,2]. They produce their effects by action on central nervous system (CNS), however, their mechanism of action not yet understood. There are many theories, which explain the mechanism of action or the clinical uses of muscle relaxants. One of these theories is that they reduce skeletal muscle spasm, possibly through an atropine like central action on cerebral motor centers or on the medulla but they do not have analgesic activity that contribute to their effects in patients with skeletal muscle spasm [3]. Anticholinergic drugs (Antimuscarinic drugs) were the most effective drugs for treatment of Parkinson's disease for more than a century, this is by blocking Acetyl choline receptors of the CNS, there by partially redressing the imbalance created by decreasing dopaminergic activity [4], however, the introduction of the dopaminergic drugs (Levodopa & decarboxylase inhibitors) has relegated anticholinergics to a supportive role in the treatment of the disorder. Nevertheless, the anticholinergic

drugs are still useful for patients with minimal symptoms as patients unable to tolerate levodopa because of side effects or contraindications, for those who are not benefited by levodopa [5] & for patients who had parkinsonian symptoms induced by antipsychotic drugs [6]. Orphenadrine citrate is white or almost white, odorless or almost odorless, crystalline powder with a bitter taste & followed by sensation of numbness. It melts in the range of 134 to 138 °C. Sparingly soluble in water, slightly soluble in ethanol; practically insoluble in chloroform and ether. It should be stored in tight & light resistant containers. Orphenadrine citrate is used for symptomatic treatment of Parkinson's disease, to relieve pain due to spasm of voluntary muscle and as an alternative to quinonin treatment of nocturnal leg cramps [7]. Orphenadrine may also be used in vertigo in patient with spontaneous vestibular disease, and it may be combined with haloperidol in treatment of chronic schizophrenic patient or with paracetamol in treatment of Myalgia. Orphenadrine is contraindicated in patient with glaucoma, elderly

people and with antacid. Its overdose is treated with physostigmine or tetrahydroaminocrine [8]. on the other hand, Orphenadrine intoxication is potentiated by ethanol and its use may cause dependence. This study was carried out to formulate Orphenadrine citrate as a tablet dosage form, through preparing different formulas, and comparing them with reference tablets. Also the effect of excipients type (binders, disintegrants and diluents) on physical properties of the tablet was studied in addition to the effect of incorporation method of disintegrants. Furthermore, the selected formula, which fitted the standard requirements, was thoroughly investigated for its expiration date and clinical effects.

MATERIALS AND METHOD

Orphenadrine citrate powder, Starch, Polyvinyl pyrrolidone (PVP, K30, Magnesium stearate. Dry granulation method was followed. The main steps were weighing, mixing, sieving and compression. Tablets different formulas (Table 1) were prepared to find the most satisfactory formula using wet granulation technique except formula 7 which was prepared by direct compression technique. The drug and excipients (except lubricant) were dry blended for at least 5 minutes. Then mixture was compressed into tablets using tablet machine with a single 7 mm normal concave punches.

Table 1: Different formulas of formulation of orphenadrine citrate tablets.

Composition	1	2	3	4	5	6	7	8	9
Orphenadrine citrate (mg)	75	75	75	75	75	75	75	75	75
PVP 10% w/v in ethanol	8	8		8	8	8			
Avicel pH 101	20.5	20.5	20.5	20.5				20.5	20.5
Starch	45		45		45	45	4.8	45	45
Magnesium stearate	.15	1.5	1.5	1.5	1.5	1.5	1.7		
Dextrose	45								
Acacia 20%		8							
Mannitol			45						
Explotab				20.5					
Starch disintegrant						20.5			
Emcompress							68.5		
Starch paste								8	
CMC									8
Total Weight	150	150	150	150	150	150	150	150	150

Evaluation and Testing of Extended Release Formulation

The physical evaluation tests for the extended release tablets were performed and mean values were calculated.

Evaluation of tablets (*in-vitro* testing). Basically, there are two types of test for evaluation of tablets [9].

Tablets Hardness

Five tablets were randomly selected from first batch and crushing strength of each tablet was measured using Monsanto hardness tester. The mean hardness of five tablets was determined and expressed in Kg/cm². The hardness of orphenadrine citrate tablets were measured using Monsanto hardness testers normal range between 5 to 8 kg [10]. Take average hardness.

Friability Test

It is performed to check whether the tablets we made can withstand any kind of fracture or breakage during packing or transportation [11].

Twenty tablets are weighed and placed in the friabilator operated at 25 rpm for 4 minutes. The tablets are then dedusted and weighed. The difference in the two weights is used to calculate friability and the value of friability is expressed in percentage. It is determined by the following formula:

$$\text{Friability} = (Iw - Fw)/Iw \times 100\%$$

Where,

Iw = Total Initial weight of tablets;

Fw = Total final weight of tablets.

Tablet Thickness

Tablet thickness is an important QC test for tablet packaging. Very thick tablet affects packaging either in blister or plastic container. Tablet thickness is set by the die of the tablet.

Weight Variation Test

Weight variation analysis was done by weighing 20 tablets individually, the average weight was calculated and % variation of each tablet from the average weight of tablets was calculated [12].

According to the USP weight variation test is run by weighing 20 tablets individually calculating the average weights and comparing the individual tablet weights to the average. The value of weight variation test is expressed in percentage. The following formula is used:

$$\text{Weight Variation} = (Iw - Aw)/Aw \times 100\%$$

Where,

Iw = Individual weight of tablet;

Aw = Average weight of tablet.

As per USP the tablet complies with the test if not more than 2 of the individual masses deviate from the average mass by more than the percentage deviation as shown in Table 1 and none deviates by more than twice that percentage.

Disintegration Test

Start the disintegration test on 6 tablets from every batch accordingly. Put water of $37 \pm 2^\circ\text{C}$ into the beaker of 1000 ml. Fix the basket to the disintegration tester and place the beaker with water. Adjust the water level to achieve the bottom of basket being 15-20 mm below the water level at the top dead center movement of the basket. Set the motor rotation speed to the minimal value (30 rpm). Insert the tablet, turn on the motor and begin to measure the disintegration time. Observe visually the course of the test. The tablet complies with the test according to USP, if all of the tablets have disintegrated completely. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets. The requirement is met if not less than 16 of the total of 18 tablets tested are disintegrated [13].

Dissolution Test

The in vitro drug release study was performed using USP dissolution rate test apparatus (paddle type; 50 rpm). Dissolution study was carried out for 12 h. Phosphate buffer (pH 4.5; 900 ml) was used as dissolution media. Samples of each 5 ml were withdrawn after every 1 h for a period of 12 h. Volume in dissolution vessel was kept constant by equal replacement with fresh media. The samples were collected in test tubes after filtration through Watt Mann filter paper. The amount of the drug in the aliquots was quantified by taking the absorbance of the sample at 267 nm spectrophotometrically, using phosphate buffer pH 4.5 (dissolution media) as the blank.

Organoleptic Testing

The tablets prepared were white in colour as there is no addition of colourant in them, circular in shape, small sized of average equal thickness and approximately odourless or having slight odour.

RESULTS

The friability test was performed on prepared tablets and it was found to be 0.966% which is within the limit. The weight variation test was performed on prepared tablets and it was found to be 142.025 mg which is within the limit. The hardness test was performed on prepared tablets and it was found to be 5.304 kg which is within the limit. The thickness test was performed on prepared tablets and it was found to be 4.67 mm which is within the limit

Tablet 2: Outcomes of various evaluation parameters.

Parameters	Outcomes
Average thickness (mm)	4.67
Hardness of tablets (kg/cm ²)	6.9-8.2
Friability (%)	0.99667
Disintegration time (min)	20

Disintegration

The disintegration time of orphenadrine citrate tablet is 20 min. That is within the range according to pharmacopeia.

Organoleptic Testing

The tablets prepared were white in colour as there is no addition of colourant in them, circular in shape, small sized of average equal thickness and approximately odourless or having slight odour.

DISCUSSION

The prepared extended release tablets were evaluated for various physical parameters such as weight variation, hardness, friability and disintegration [14, 15]. All the tablets were produced under conditions to avoiding processing variables. Hardness of tablets ranged from 6.9-8.2 kg/cm² and the percentage friability was 0.99667 % with in limit of USP and the average thickness of tablet was 4.67. The disintegration time is 20 min and dissolution is also within the range of USP criteria. From all previous project work one can conclude that best binder is PVP. It is cheap, available, compressible and compatible with drug. The best for extended release product [16, 17].

CONCLUSION

The overall findings of this study indicate that the drug can be prepared as extended release tablets, which fit the requirements of British Pharmacopoeia since the prepared tablets gave satisfactory results.

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