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Formulation and *In-vitro* Evaluation of Immediate release tablets of Drotaverine HCl

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ABSTRACT

The aim of the present study is to develop and evaluate the immediate release tablet of Drotaverine HCL. Wet granulation method was used because of very high flow of powder blend that might create the problem of uneven dye filling. The Superdisintegrant AC-Di-Sol and Crospovidone were used for immediate release of drug from tablet. The coating was done to minimize the oxidation of Drotaverine HCL. From the results, it can be concluded that increase in concentration of superdisintegrant will lead to decrease the disintegration time up to 8 min after coating without any change observed in the dissolution profile of drug.

Keywords: Drotaverine HCL, Immediate release tablet, Superdisintegrant, AC-Di-Sol, and Crospovidone.

INTRODUCTION

In current market, tablet is most widely used dosage form because of ease of administration and convenient for industry to manufacturer. In pharmaceutical industries, manufacturing of tablets are usually focused on the optimization of the excipients mixture composition to obtain a product that meet established standard [1, 2].

The tablet dosage form is a versatile drug delivery system. Different types of tablet formulations are available, which could be broadly classified based on: (1) route of administration such as tablets for oral delivery, sublingual delivery, buccal delivery, rectal delivery or vaginal delivery,

and (2) formulation characteristics such as immediate release tablets, effervescent tablets, melt-in-mouth or fast dissolving tablets, delayed release or extended release tablets. In all the cases, the general manufacturing process, machinery used for preparation of tablets and materials used are similar [3].

Immediate release solid oral dosage forms are classified as either having rapid or slow dissolution rates. Immediate release dosage forms are those for which ≥85% of labeled amount dissolves within 30 min. For immediate release tablets, the only barrier to drug release is simple disintegration or erosion stage, which is generally accomplished in less than one hour [4].

Drotaverine Hydrochloride, 1-[(3, 4-diethoxy phenyl) methylene]-6, 7-diethoxy-1, 2, 3, 4-tetra hydro iso-quinolene is an analogue of papaverine. It is an antispasmodic agent without the Anti-cholinergic side-effects which act by inhibiting phosphodiesterase IV enzyme, specific for smooth muscle spasm and pain, used to reduce excessive labor pain. While the other antispasmodic agents like Dicyclomine, Oxybutylin, Flavoxate, Pirenzepine, etc. have anticholinergic side-effects. Drotaverine hydrochloride is official in Polish Pharmacopoeia. It is currently used successfully in many countries for treating renal colic. A multicentre, placebo controlled, Randomized, double-blind study used drotaverine to control the acute Episode on arrival to hospital [5-8]. It causes smooth muscle relaxation by increasing intracellular levels of cyclic adenosine mono-phosphate (cAMP) secondary to inhibition of phosphodiesterase. Drotaverine has been shown to inhibit platelet aggregation in a dose dependent manner [9].

Azhlwar *et al.* (2010) studied a Simultaneous densitometric analysis of Drotaverine and Aceclofenac by HPTLC method. Use of methanol-ethyl acetate-glacial acetic acid 1:9:0.01 (v/v/v) gave good separation for the two drugs. The R_f values were 0.18±0.02and 0.51±0.02, respectively, for drotaverine and aceclofenac [21]. Pareek A. *et al.* (2010) evaluated the efficacy and safety of aceclofenac-drotaverine combination against aceclofenac alone in patients with primary dysmenorrhoea [22]. Prasad R. K. *et al.* (2010) studied spectrophotometric Quantitative Estimation and Validation of Nimesulide and Drotaverine Hydrochloride in Tablet Dosage form [23]. Prasad P.D. *et al.* (2009) developed a reverse phase HPLC method for the quantitation of drotaverine hydrochloride and mefenamic acid in human plasma [24]. Parmar J. *et al.* (2009) described tablet Formulation Design and Manufacture of Oral Immediate Release Application [25]. Rajmane S.V. *et al.* (2009) determined Drotaverine Hydrochloride and Aceclofenac in tablet dosage form by Spectrophotometry. λ-max for Drotaverine hydrochloride and Aceclofenac is 242 nm and 273 nm respectively. Both the drugs obey Beer's law in the concentration range 10-50 µg/ml [26].

Proctor M. *et al.* (2006) studied diagnosis and management of dysmenorrhoea. Randomized controlled trials are ongoing currently on antispasmodics (drotaverine hydrochloride) [27]. Kim A.A. *et al.* (2005) developed a radiochemical method of measurement of binding drotaverine hydrochloride with human blood serum albumin [28]. Romics I. *et al.* (1992) studied the effect of drotaverine hydrochloride in acute colicky pain caused by renal and ureteric stones. Intravenous drotaverine provides effective pain relief in more than two-thirds of patients with renal colic, with no serious side-effects [29].

EXPERIMENTAL SECTION

Materials

Drotaverine HCl was obtained as gift sample from Ra Chem Pharma Ltd., Hyderabad. All other chemicals and reagent used were either analytical or pharmaceutical grades. Lactose monohydrate was purchased from Lactose India Ltd., Ac-Di-Sol from FMC biopolymer, Cross Povidone from Nanhang industries, Aerosil-200 from Evonik Degussa, Stearic Acid (Micronized) from Tauras Chemicals, HPMC 5cps from Taiwan Ruital cellulose Ltd., Titanium dioxide from Hundman Ti-oxide, Purified talc from Vijay minerals, Ferric oxide yellow from BASF.

Methods

Evaluation of Powder Blend [4]

A) Bulk Density (D_b): It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted. This initial volume was called the bulk volume. From this the bulk density was calculated according to the formula mentioned below. It is expressed in gm/ml and is given by

$$D_b = M / V_b$$

Where, M and V_b are mass of powder and bulk volume of the powder respectively.

B) Tapped Density (D_t): It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times and the tapped volume was noted if the difference between these two volumes is less than 2%. If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2 % (in a bulk density apparatus). It is expressed in gm/ml and is given by

$$D_t = M / V_t$$

Where, M and V_t are mass of powder and tapped volume of the powder respectively.

C) Flow properties of blend [13]: The flow properties of blend (before compression) were characterized in terms of angle of repose, Carr's index and Hausner ratio. For determination of angle of repose (θ), the blend were poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2.0 cm above hard surface. The blends were poured till the time when upper tip of the pile surface touched the lower tip of the funnel. Angle of repose was calculated using following equation.

$$\tan \theta = (h/r)$$

Where, h = height of pile; r = radius of pile

D) Carr's index (or) % compressibility [11]: It indicates powder flow properties. It is expressed in percentage and is given by

$$\textbf{C.I.} = D_t - D_b / D_t * 100$$

Where, D_t and D_b are tapped density and bulk density respectively.

E) Hausner ratio: Hausner ratio is an indirect index of ease of powder flow. It was calculated by the following formula.

$$\textbf{Hausner ratio} = D_t / D_b$$

Where, $\mathbf{D_t}$ and $\mathbf{D_b}$ are tapped density and bulk density respectively.

Preparation of tablets [12]

Sifted Drug with Lactose Monohydrate through 40# and mixed well. Binder solution was prepared by dissolving BHT in IPA than add Methylene chloride, further dissolved Ethyl cellulose in the above binder solution. The drug-diluent mixture was then hand granulated by adding binder solution in it. The granules were kept for drying in Tray dryer. Passed the dried granules through 20# and check the LOD. For lubrication, passed Ac-di-sol, Cross Povidone, and Aerosil-200 through 40# and mixed with dried granules. Then separately passed Stearic acid through 40# and mixed it in above dried granules. The above dried granules were subjected to compression. Compression was done on 16 station B tooling single rotary machine, using Standard concave 8.0 mm punch plain on both sides.

Preparation of coating solution [14]

HPMC 5cps, Titanium dioxide and Purified talc were dissolved in IPA with continuous stirring. Di-butyl-pthalate was dissolved separately in Methylene chloride. Both the solution were mixed and kept for stirring for 10 minutes. The color was added into above solution. Homogenization of the solution was done for 15 min (table.1).

Table 1: Drug-Excipients Ratios in Trials

Ingredients	**Trial-1**	**Trial-2**	**Trial-3**
Drotaverine HCl	83.33	83.33	83.33
Lactose monohydrate	43.49	42.67	39.97
Ethyl cellulose	4.0	4.0	4.0
Butyl Hydroxy toluene	1.0	1.0	1.0
IPA	q.s	q.s	q.s
Methylene Chloride	q.s	q.s	q.s
Ac-Di-Sol	2.82	3.50	5.64
Cross Povidone	2.82	3.50	4.23
Aerosil-200	0.71	1.0	0.71
Stearic Acid	2.82	2.0	2.11
Average weight	141.00	141.00	141.00
Coating materials			
HPMC 5cps	7.00	7.00	7.00
Titanium dioxide	1.12	1.12	1.12
Purified talc	0.94	0.94	0.94
Ferric oxide yellow	0.25	0.25	0.25
Dibutyl Phthalate	0.70	0.70	0.70
IPA	q.s	q.s	q.s
Methylene chloride	q.s	q.s	q.s
Average weight	151.00	151.00	151.00

Coating of tablet [15]

Coating parameters were set as Pan Speed at 8 rpm with the Temperature of 40 □C. the spray rate were kept at 2 rpm[15].

Calculations

A trial batch of 1000 tablet of 80 mg was decided to be prepared.

Raw material calculation

Drotaverine HCl = Label claim × (100/assay) × (100/100-LOD)
= 80 × (100/100) × (100/100-4.0)
= 83.33mg/tab
{Because, assay of drug=100.2 & LOD = 4.0%}

Evaluation of Immediate release Tablets [10]

Tablets were evaluated for hardness, weight variation, friability, thickness, and disintegration time (table.3, 4 & 5).

A) Weight variation test

The variation of weight of individual tablet is a valid indication of the corresponding variation in the drug content [10]. Twenty tablets were selected at random and their average weight was determined using an electronic balance (Metler Toledo). The tablets were weighed individually and compared with average weight.

B) Hardness determination

The hardness of three tablets from each batch was measured by using hardness tester (Monsanto hardness tester).

C) Friability test [18]

Friability was determined taking 20 tablets. Tablets samples were weighed accurately and placed in Roche's Friabilator. After the rotations at given specifications (100 revolutions at 25 rpm), loose dust was removed from the tablets. Finally tablets were weighed and determine the friability.

D) Disintegration test [16]

Disintegration was evaluated to ensure that the drug substance is fully available for dissolution and absorption from the gastrointestinal tract. In disintegration test, measured using USP tablet disintegration test apparatus (ED2L, Electrolab, India) using 900 ml of distilled water without disk at room temperature (37±20C).

E) Assay [17]

It has been reported that Drotaverine HCl can be detected at 242 nm. Twenty tablets were powdered, and powder weight equivalent to 10 mg of Drotaverine was accurately weighed and transferred into a 100 ml volumetric flask. Initially, 10 ml of 0.01N HCL was added and shaken for 10 min. Then, the volume was made up to 100 ml with same solution. The solution in the volumetric flask was filtered, diluted suitably and analyzed spectrophotometrically at 242 nm.

F) Dissolution study [19, 20]

Dissolution test of Drotaverine tablets was performed using USP dissolution testing apparatus 2 (Paddle method; Electrolab TDT-08L). The dissolution test was performed using 900 ml of 0.01N HCL at 37 ± 0.5°C and 100 rpm, using a Shimadzu UV/Vis double beam spectrophotometer. Test sample (5 ml) was withdrawn at particular time interval (45 and 60 minutes) and replaced with fresh dissolution media maintained at 37 ± 0.5 C. The test sample was filtered (membrane filter, 0.45 μm) and the concentration of drug determined using UV spectrophotometer at λ-max 242 nm. This test was performed on 6 tablets and mean ± SD calculated.

RESULTS AND DISCUSSION

The formulation was undertaken with the aim to formulate and evaluate Drotaverine Immediate Release Tablet. Formulation of tablet was done by wet granulation technique because the flow properties of the powder blend (table.2) was excellent and to minimize the weight variation, improper dye filling problems. That's why the selection of excipient like Lactose monohydrate was based on wet granulation. The flow property of the granules was determined from the angle of repose. Values of angle of repose was found in the range of 26-31 (table.2).

Table 2: different evaluation results of powder blend & granules

Blend / Trials	Blend	Trial-1	Trial-2	Trial-3
LOD % (w/w)	0.23	1.13	0.99	3.01
Bulk Density (gm/ml)	0.754	0.464	0.459	0.560
Tapped Density (gm/ml)	0.793	0.555	0.565	0.700
Angle of Repose	18	26	31	28
% Compressibility Index	4.918	18.43	15.49	20.00
Hausner ratio	1.052	1.330	1.326	1.250

Carr's index and Hausner ratio were in the range of 15-20 and 1.25-1.33 respectively (table.2). Hence the prepared granules have good flow property and can be used for tablet manufacturer.

Trial-1 was formulated using antioxidant BHT, Ethyl cellulose as a binder which also preventing oxidation of drug (table.1). In this Ac-di-sol and crospovidone were used as disintegrating agents. In this disintegration time after coating was found above to limit (table.3 & 4).

Table 3: Physical Parameter Of Uncoated Tablet

Trial No	Thickness (mm)	Hardness (N)	Disintegration time (min)	Assay (%)
1	3.37	95-123	15	98
2	3.36	95-124	12	97
3	3.38	95-125	7	99

Table 4: Physical Parameter of Coated Tablet

Trial No	Thickness (mm)	Hardness (N)	Disintegration time (min)	Assay (%)
1	3.44	98-129	17	97
2	3.45	98-129	14	98
3	3.42	98-129	8	99

In Trial-2, the concentration of both disintegrating agents was increased. But in this trial, DT was observed quite above the limit after coating. So again concentration increased in next trial-3.

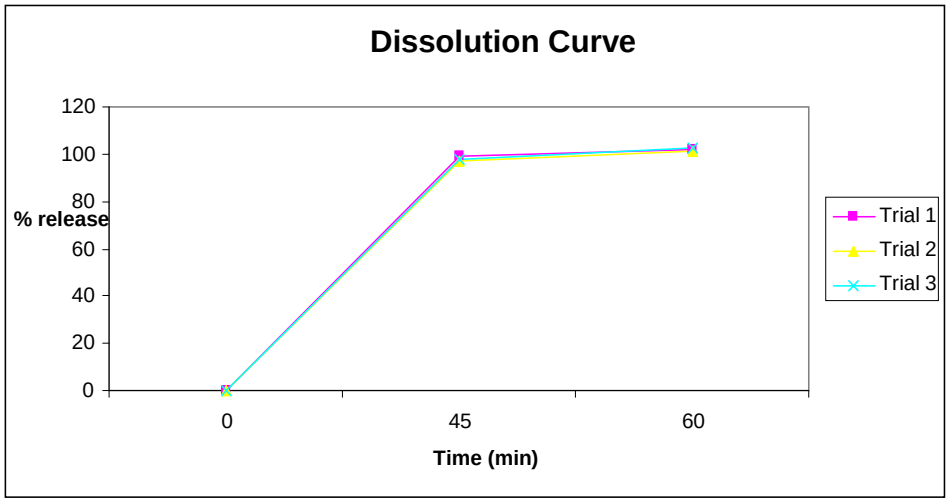

Figure 1: Dissolution Profile of Drotaverine. HCl

Table 5: Dissolution Profiles of All Batches

Sr. No	Time (min)	Trial-1	Trial-2	Trial-3
1	0	0	0	0
2	45	99	97	98
3	60	102	101	103

In this trial-3, the concentration of disintegrating agents was further increased. The satisfactory results were found in trial-3. It was clearly observed, that dissolution profile (table.5 & fig.1) not changed on increasing the concentration of disintegrants in three consecutive batches. It was observed that increasing the concentration of both disintegrant will decrease the disintegration time.

CONCLUSION

From the present study of development and evaluation of Drotaverine HCl immediate release tablets, it can be concluded that disintegration-time depends on the concentration of Disintegrating-agents and is inversely proportional to Disintegration-time (D.T) of coated tablets. And it has no effect on release profile i.e. dissolution profile of coated tablets (fig.1). A broad

variety of drug release pattern could be achieved by variation in concentration of the polymers and disintegrants as a scope for further studies. Moreover, the work can be extended to the *in vivo* studies to conclude IVIVC. The work can be carried out to study the effect of other parameters like stability study as per ICH.

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