Process Evaluation and *In-vitro* Drug Release Study of Fast Dissolving Uncoated Tablets of Drotaverine HCl

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Abstract. Drotaverine, a selective phosphodiesterase (PDE) isoenzyme IV inhibitor. It has been found to be useful in spastic and motility disorders of the smooth muscle in adult. In the present work an attempt was made to study the screening of critical processing parameters affecting the dissolution profile of Drotaverine HCl. For Drotaverine HCl Lubrication time, milling time, and blending time was found to be effective parameter. Compression speed and compression force is also having effect on dissolution of Drotaverine HCl. The *in-vitro* drug release was carried out on the formulated tablet and compared with the marketed product.

Key words: fast dissolving tablets, drotaverine HCl & critical process parameters.

Introduction

Fast dissolving drug delivery system is Novel Drug Delivery system. The main goal for designing dosage forms, convenient to be manufacture and administer without water, free of side effects, offering instant release and improved bioavailability, so as to achieve better patient compliance. This segment of formulation is particularly designed for pediatric, geriatric, bedridden, psychotic patients who are unable to swallow or refuse to swallow conventional oral formulation and also for active patients who are busy and traveling and may not have access to water (Patel et al., 2014: 30). The main aim of design fast dissolving tablets is to increase the bioavailability of the poorly soluble drugs. These are conveniently administrable to the pediatric and geriatric patients who are suffering from swallowing of solid dosage forms orally (Chirravuri et al., 2016: 3-7; Soni and Singhai, 2013: 5-13). Drotaverine hydrochloride, 1-[(3, 4-diethoxy phenyl) methylene]-6, 7-diethoxy-1, 2, 3, 4-tetra hydroisoquinolene is an analogue of papaverine (Alderman, 1984: 9). It is phosphodiesterase IV enzyme inhibitor and acts as an antispasmodic agent, specific for smooth muscle spasm and pain, used to reduce excessive labor pain (Alderman, 1984: 9) (Fig. 1).

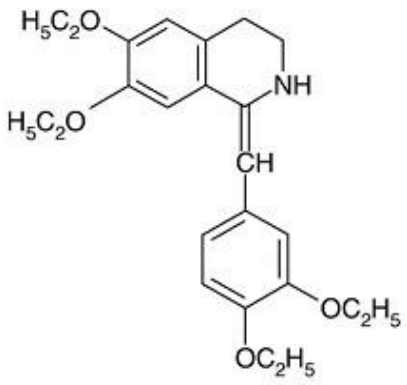

Fig. 1. Structure of Drotaverine

In the present work an attempt was made to study the screening of critical processing parameters affecting the dissolution profile of Drotaverine HCl.

Material and Methodology

Procurement of Drug: Drug (Drotaverine hydrochloride) was obtained as a gift sample from Provizer Pharmaceutical, Surat.

Preparation of Tablets

Drotaverine HCL tablets were formulated as per the formula given in the Table 1. Each tablet was of 145 mg containing 80mg of the drug and rest excipients. The granules were kept for drying in FBD. The granule was mixed in appropriate quantities of talc (as glidant) and magnesium stearate (as a lubricant and antiadherent). The above dried granules were subjected to compression. Compression was done on 27 station B tooling single rotary machine, using Standard concave 8.0 mm punch plain on both sides (Table 2).

Table 1. Core tablets were formulated as per formula

S.no	Ingredient	Quantity (mg/tablet)
1	Drotaverine HCl	83.3
2	Lactose monohydrate	34.1
3	Ac-Di-Sol	5.6
4	Cross Povidone (CP)	2.8
5	PVP K 30	6.6
6	Sodium starch glycolate	6.6
7	Magnesium stearate	4.4
8	Methylene Chloride	q.s.
Total		143.6

Table 2. Critical process parameters considered for study

Dry mixing	Batch size	250.00 gm
	Batches taken for study	F1, F2, F3, F4, F5
	Variable considered for study	Mixing time
	Acceptance criteria	Mixing end point by assay, bulk density, tapped density
Lubrication	Batch size	250.00 gm
	Batches taken for study	F1, F2, F3, F4, F5
	Variable considered for study	Blending time
	Measure response	Assay, Tapped density, Bulk density, Angle of repose
	Acceptance criteria	Free flowing powder blend with no lumps
Compression	Type of machine	27 station single rotary compression machine
	Type of machine	Compression force and Machine speed

Dissolution Study

In- vitro drug release study

In-vitro drug release studies were carried out using USP XXVII dissolution apparatus type II at 50 rpm. The dissolution medium consisted of 900ml of 0.1N HCl (pH 1.2), maintained at 37±0.5^{0}C. The dissolution samples were collected at every 1-hour interval and replaced with an equal volume of 0.1N HCl to maintain the volume constant. The sample solution was dilute sufficiently and analyzed at 264 nm using an UV spectrophotometer (Gupta and Gaud, 1999: 229-234).

Table 3. Dissolution profile for in-vitro drug release

S. No.	Conditions	Parameters
1.	Dissolution Apparatus	Electrolab TDT-08L
2.	Dissolution Media	0.1N HCl (pH 1.2)
3.	Volume of Media	900 ml
4.	Sampling Volume	1 ml
5.	Volume replaced after sampling	1 ml
6.	Rotation Speed	50 rpm
7.	Temperature	37±5ºC
8.	λ_{max}	264 nm
9.	Beer's Range	2-10 µg/ml

Result and Discussion

The *in-vitro* drug release was carried out on the formulated tablet and compared with the marketed product. Studied suggest that amongst all the formulation F2 exhibited the best release profile and releasing approximately 98.5% drug in 60 min. The results were tabulated in Table 4-9 and Fig. 2-6.

Table 4. In Vitro Dissolution Profile of Batch F1

Batch	Time	DROTAVERINE HCL						
		5	10	15	20	30	45	60
F1	Tablet -1	17	23	46	62	82	89	95
	Tablet-2	13	29	41	66	83	88	97
	Tablet-3	12	33	50	64	89	92	98
	Tablet-4	16	35	52	63	88	93	97
	Tablet-5	18	30	46	60	84	90	94
	Tablet-6	19	31	49	62	80	86	96
	Mean	15.83	30.16	47.33	62.83	84.33	89.66	96.16

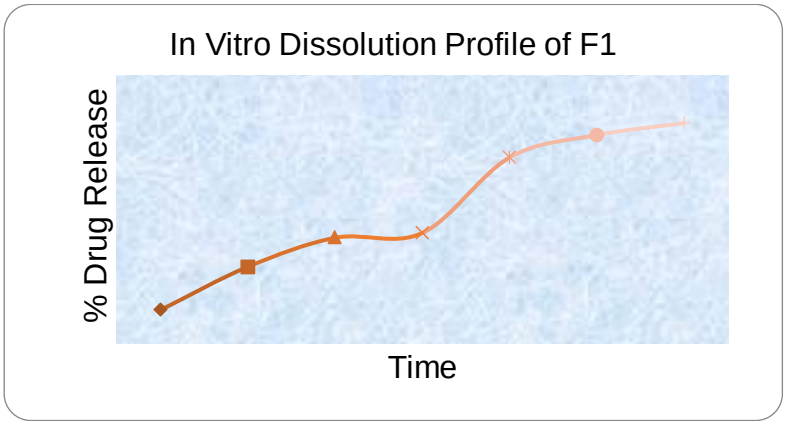

Fig. 2. In Vitro Dissolution Profile of Batch F1

Table 5. In Vitro Dissolution Profile of Batch F2

Batch	Time	DROTAVERINE HCL						
		5	10	15	20	30	45	60
F2	Tablet -1	11	24	38	46	84	88	98
	Tablet-2	16	33	46	49	83	96	97
	Tablet-3	15	35	41	46	80	90	100
	Tablet-4	14	40	50	46	86	95	99
	Tablet-5	16	36	56	54	82	96	98
	Tablet-6	17	37	52	50	84	94	99
	Mean	14.83	34.16	47.16	49.33	83.16	93.16	98.5

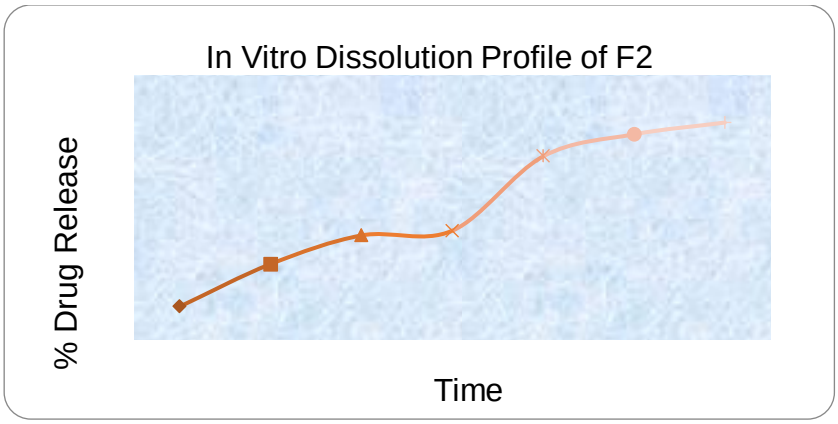

Fig. 3. In Vitro Dissolution Profile of Batch F2

Table 6. In Vitro Dissolution Profile of Batch F3

Batch	Time	DROTAVERINE HCL						
		5	10	15	20	30	45	60
F3	Tablet -1	10	22	40	52	82	87	92
	Tablet-2	16	32	43	54	86	90	96
	Tablet-3	15	33	46	55	86	92	94
	Tablet-4	14	33	55	56	87	90	98
	Tablet-5	16	36	55	54	80	91	96
	Tablet-6	18	38	58	57	86	95	98
	Mean	14.83	32.33	49.5	54.66	84.5	90.83	95.66

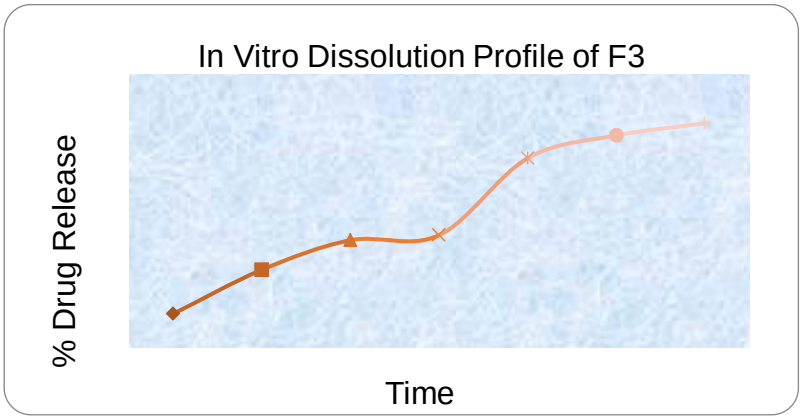

Fig. 4. In Vitro Dissolution Profile of Batch F3

Table 7. In Vitro Dissolution Profile of Batch F4

Batch	Time	DROTAVERINE HCL						
		5	10	15	20	30	45	60
F4	Tablet -1	15	19	38	45	64	78	82
	Tablet-2	12	24	40	48	60	72	85
	Tablet-3	11	30	33	46	65	77	87
	Tablet-4	13	32	41	50	68	80	90
	Tablet-5	9	25	46	48	67	76	92
	Tablet-6	10	33	37	51	69	79	89
	Mean	11.66	27.16	39.16	48.5	65.5	77	87.5

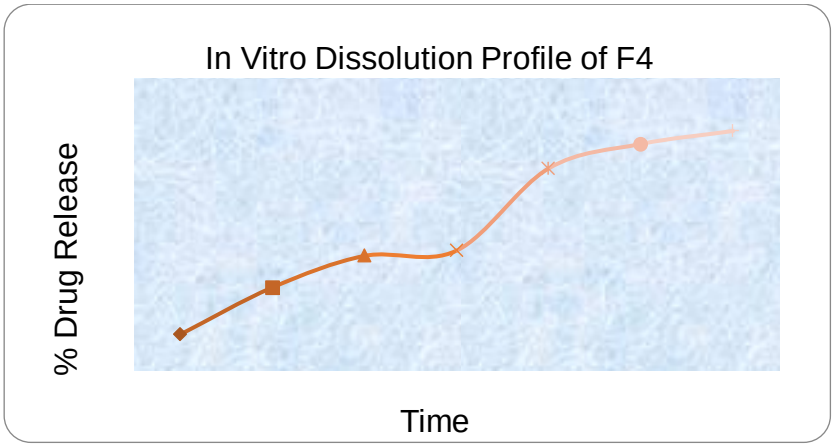

Fig. 5. In vitro Dissolution profile of Batch F4

Table 8. In Vitro Dissolution Profile of Batch F5

Batch	Time	DROTAVERINE HCL						
		5	10	15	20	30	45	60
F5	Tablet -1	10	15	25	26	38	50	76
	Tablet-2	12	16	24	28	40	55	78
	Tablet-3	11	18	30	30	42	58	75
	Tablet-4	14	20	28	35	45	59	78
	Tablet-5	16	24	30	40	47	62	80
	Tablet-6	20	26	32	42	50	65	82
	Mean	13.83	19.83	28.16	33.5	43.66	58.16	78.16

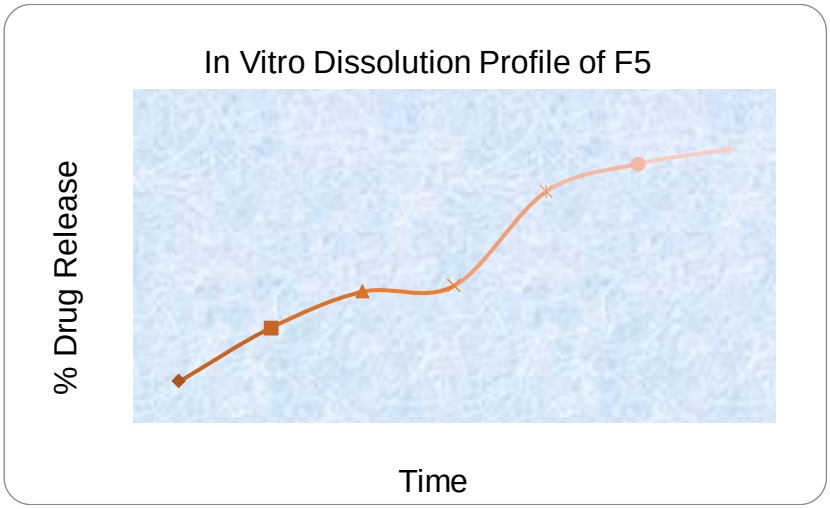

Fig. 6. In Vitro Dissolution Profile of Batch F5

Table 9. In Vitro Dissolution Profile of Batch F2and Drotin (Marketed formulation)

Tablet	Time						
	5	10	15	20	30	45	60
F2	14.83	34.16	47.16	49.33	83.16	93.16	98.5
Drotin	15.66	28.70	42.78	54.26	65.60	85.87	98.30

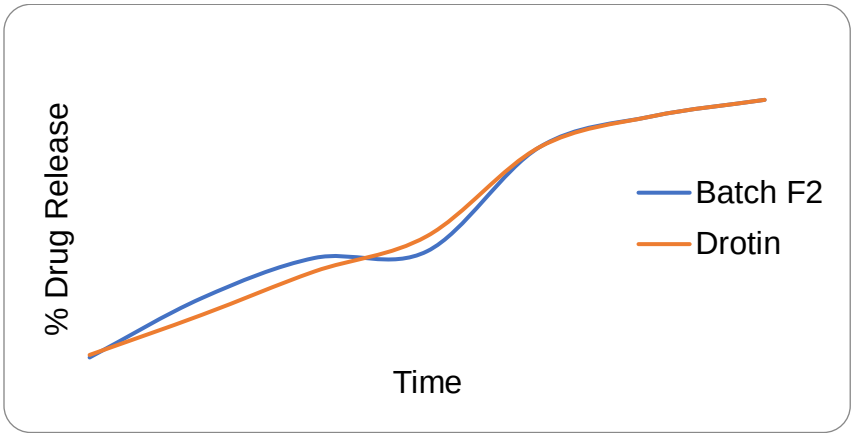

Fig. 7. Comparison of Dissolution profile of F2 with marketed formulation (Drotin)

Further the dissolution profile of formulation F2 was compared with marketed tablet (Drotin).

This study represents that Disintegration time of Drotaverine HCl can be improve with the help of superdisintegrant Ac-Di-Sol, which is best superdisintegrant cross linked Sodium Carboxymethylcellulose. It is effective at very low concentration has enhanced long term stability and facilitates quick disintegrantion and dissolution in drotaverine HCl tablet granules and other dosage form.

This study also presents that the screening of critical processing parameters affecting the dissolution profile of Drotaverine HCl. For Drotaverine HCl Lubrication time, milling time, and blending time was found to be effective parameter. Compression speed and compression force is also having effect on dissolution of Drotaverine HCl. The blending step discussed here is considered critical to the quality of the product. The

parameters that can significantly affect the time to the endpoint of the process are environmental humidity & Particle size of the API and MCC. Table 10, 11 exemplify the input attributes that are known to produce blend of acceptable quality.

Table 10. Evaluation of Parameters at Drying

S.No	Parameter	Severity of the parameter for dissolution
1	Inlet air temperature not within the specified limits	Medium
2	Sieve integrity of finger bag not proper	Low
3	Non-uniformity of Drying	Medium

Table 11. Input attributes for Blending Operation

Input Attributes	Range
Humidity	20-70% RH
API	10-40 µ
MCC	30 - 90 µ
Equipment	Any diffusive blender
Lactose	70 – 100 µ

Pre lubrication mixing time has positive effect on MDT, as the pre lubrication mixing time increases, more uniformly binder mix in the powder. Lubrication time has positive effect on MDT, as the lubrication time increases, MDT increases due to low dissolution, because as the lubrication mixing time increasing, more uniformly lubricant mix in the powder (Table 12).

Table 12. Evaluation at Lubrication stage

S.No	Parameter	Severity of the parameter for dissolution
1	Pre lubrication Mixing Time	High
2	Effect of Lubrication Time	High

Compression speed has negative effect on Mean Dissolution time. As the compression speed increases, MDT decreases due to higher dissolution. This was due to low stay time of tablet. So hardness decreases. So ultimately dissolution of drug increases. Different compression force has been found to possess a great impact on the release characteristics and found significantly affect on release rate. It was observed that at a constant die fill, an increase in the compression force to a certain limit results in a proportional increase in tablet hardness and decrease in tablet thickness (Table 13).

Table 13. Evaluation at Compression stage

S.No	Parameter	Severity of the parameter for dissolution
1	Compression Speed	High
2	Compression force	High

For all the batches, the speed of Double cone blender was kept at 25 rpm and samples were drawn at time interval of 5, 10, 15 and 20 minutes till the uniform distribution of all content was achieved (Table 14).

Table 14. Assay of samples drawn during blending at different time

Batch	05 min	10 min	15 min	20 min
F1	86.52	93.78	98.92	101.95
F2	88.06	93.72	96.94	99.30
F3	89.98	94.21	99.74	99.78
F4	89.35	95.56	100.02	101.44
F5	86.76	93.81	98.24	100.78

The lubrication process was carried out with required quantity of lubricant at speed of 25 rpm for 5, 10, 15 and 20 min (Table 15).

Table 15. Assay of Samples drawn during lubrication

Batch	05 min	10 min	15 min	20 min
F1	99.01	98.59	98.60	98.46
F2	99.25	101.20	99.78	99.06
F3	100.04	99.20	99.90	99.64
F4	99.36	101.10	99.86	97.98
F5	100.91	100.22	100.56	99.80

Conclusion

From this study, it can also be concluding that without making changes in formulation composition, only by changing the processing parameters we can change the dissolution rate of the drug. So that burden on polymers can be reduced and it will be cost effective to sustained the release of water soluble drug.

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