ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Formulation and Evaluation of Floating Drotaverine Hydrochloride Tablets Using Factorial Design

Om Prakash*, S Saraf, M Rahman, Neeraj Agnihotri, and Vinay Pathak

Department of Industrial chemistry, Integral University, Lucknow. Uttar Pradesh, India.

ABSTRACT

The main aim of this study was to optimize and evaluate the floating tablets of Drotaverine HCl that prolong the gastric residence time, increasing drug bioavailability and control pain for longer duration by oral administration. A floating drug delivery system(FDDS) was developed using gas forming agent like sodium bicarbonate, citric acid polymers like hydroxypropyl methyl cellulose(HPMC), Sod CMC, Carbopol-934P, PVP K-30. In 3^2 factorial design amount of HPMC(X1) and gas generating agents(X2) were selected as independent variable and % drug release for 30min,1h, 2h,4h,6h, 8h,12h, 16h , 24h and floating lag time (FLT) were taken as dependent variable. The floating tablet formulations were evaluated for Bulk density (gm/cm3), Tapped density(gm/cm3), Hausner ratio(HR), Carr index, Angle of repose, flow property, assay, *in-vitro* drug release, hardness, friability,weight variation. The results of *in vitro* release studies showed that the optimized formulation (F9) could sustain drug release (98.74%) for 24h and remain buoyant for more than 24h. The combination of hydrophilic (HPMC) and hydrophobic (carbopol-934P) polymer provides a better option for 24h release action, bioavailability, stability of tablets at 40^{0C}/75%RH, of optimized formulation was carried for one month and no significant change was observed.

Keywords: floating drug delivery system(FDDS), Drotaverine HCl, gas generating agents, floating lag time (FLT), hydrophilic (HPMC) and hydrophobic (carbopol-934P) polymer.

Corresponding author

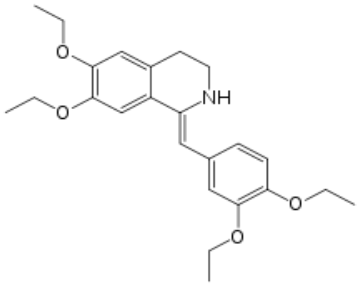
ISSN: 0975-8585

INTRODUCTION

Gastroretentive dosage forms, i.e. those designed to exhibit a prolong gastric residence time (GRT), have been a topic of interest in terms of their potential for controlled drug delivery (L. Whitehead et al 1998). Pain is a warning signal (Tripathi K.D 2004), primarily protective in nature but causes discomfort and suffering, may even be unbearable & incapacitating, i.e. pain is an ill-defined, unpleasant sensation, usually evoked by an external or internal noxious stimulus. Excessive pain may produces other effects like sinking sensation, apprehension, sweating, nausea, palpitation, rise or fall in BP or tachypnoea, analgesics relieve pain as a symptoms without affecting its cause.

Pain caused by kidney stones (Renal colic pain) and Labour pain is most common and chronic pain. Renal colic pain typically begins in the kidney area or below it and radiate through the flank until it reaches the bladder. Renal colic pain tends to remain constant whereas colic implies pain that is somewhat intermittent & often comes in the waves such as in biliary colic. Depending on the type & size of kidney stones moving through the urinal tract, the pain may be stronger in the renal or bladder or equally strong in both. Childbirth (Labour or parturition) is culmination of a women pregnancy or gestation period with birth of infant from uterus. Hormones & enzymes work together to produce ligamentous relaxation and widening of the pubis symphysis, mostly girdle pain occurs before birthing and is known as diastasis of the pubic symphysis, pain levels reported by labouring women vary widely which seem to be influenced by fear & anxiety levels & experience with pror childbirth.

DROTAVERINE HCl [(Z)-1-(3,4-diethoxybenzylidene)-6,7-diethoxy-1,2,3,4-tetrahydoisoquinoline]



Empirical Formula: $C_{24}H_{31}NO_4$
Molecular Weight: 397.507 g/mol

Drotaverine HCl is a benzylisoquinoline derivative,and is an analogue of papaverine(Opium alkaloid) which is an antispasmodic drug acts by phosphodiesterase- IV inhibition to increases the intracellular level of cyclic adenosine monophosphate (cAMP) which causes relaxation of smooth muscle that suppress the pain associated with spasm caused by smooth muscle contraction, specially in tubular organs like stomach, intestine, ureter, urinary bladder, cholecystalgia, chronic cholecystitis, neck of uterus spasm during delivery and also used as a cerebral & coronary vasodialator in subarachnoid haemorrhage, coronary artery bypass surgery and microsurgery (Singh KC et al 2004 and Drach GW et al 1998).

ISSN: 0975-8585

MATERIAL AND METHODS

Materials

Drotaverine HCl gift sample was kindly provided by Aurochem Pharmaceuticals (I) Pvt Ltd. Mumbai -India, all other chemicals,solvents and reagents were of the analytical grade available from local sources. hydroxypropyle methyl cellulose(HPMC), Sod Carboxy methyl cellulose (SodCMC), Poly vinyl pyrrolidine (PVP) K-30,are purchase from Hi-Media, Carbopol-934P, sodium bicarbonate, citric acid procured by S.D.Fine Chem Ltd.

Methods

Experimental Design

Factorial design is an experimental design technique, from which the factor involved and its relative importance can be assessed. In the present study a 3^2 factorial design (Dalavi V.V et al 2009), was employed containing 2 factors evaluated at 3 levels (Table 1). The experimental trials were performed at all possible 9 combinations. HPMC(X1) and gas generating agents(X2) were selected as 2 independent variable and % drug release for 30min,1h, 2h,4h,6h, 8h,12h, 16h ,24h and floating lag time (FLT) were as dependent variables.

Table 1: A 3^2 full factorial design and level of independent variables

Trial No.	Coded value(X1)	Coded value(X2)
F1	-1	-1
F2	0	-1
F3	+1	-1
F4	-1	0
F5	0	0
F6	+1	0
F7	-1	+1
F8	0	+1
F9	+1	+1

Table 1.1: Independent variables

Coded value	X1	X2
-1	180	70
0	195	85
+1	210	100

X1 is amount of HPMC in mg, X2 is amount of sodium bicarbonate in mg

ISSN: 0975-8585

Formulation

Floating tablets of drotaverine HCl were prepared by wet granulation technique. All the ingredients (except mag.stearate and talc) were weighed accurately and mixed thoroughly for 30 min. using glass mortar and pestle. Granulation was done with a solution of PVP K-30 in sufficient isopropyl alcohol by passing wet coherent mass through a BSS #18 sieve. Granules were dried in hot air oven at 45^0C, dried granules were sieved through BSS # 22/44 mesh then lubricated with magnesium stearate and talc. Granules are compressed on a single punch tablet machine. The tablets were round and flat with average diameter 11.0±0.1 mm.

Table 2: COMPOSITION OF ALL THE FORMULATION (batch F1 to F9)

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drotaverine HCl	80	80	80	80	80	80	80	80	80
HPMC	180	195	210	180	195	210	180	195	210
Carbopol 934P	30	30	30	30	30	30	30	30	30
Sodium bicarbonate	70	70	70	85	85	85	100	100	100
Citric acid	50	50	50	50	50	50	50	50	50
PVP K-30	20	20	20	20	20	20	20	20	20
Magnesium stearate	7	7	7	7	7	7	7	7	7
Talc	3	3	3	3	3	3	3	3	3
TOTAL	**440**	**455**	**470**	**455**	**470**	**485**	**470**	**485**	**500**

PRE COMPRESSION STUDIES (R.Margret Chandira et al 2010 and B.Prakash Rao et al 2009)

Bulk density (dB)

Density is determined by dividing weight of powder by volume of powder in g/cm3. Bulk density is determined by weight of dry powder and the bulk volume in a graduated cylinder.

Tapped density (dT)

Tapped volume is measured by tapping of cylinder filled with bulk powder from a constant hight on flat horizontal surface for 100 times. This tapped volume gives tapped density by dividing weight of dry powder by tapped volume.

Hausner ratio

The Hausner ratio is a number that is correlated to the flowability of a powder or granular material. It is calculated by the formula HR= dT/dB . A Hausner ratio greater than 1.25 is considered to be an indication of poor flowability.

Carr index

It is also known as compressibility index.Carrs index gives the important properties of powder or granules and is calculated by following equation: CI = $\frac{dT - dB}{dT} \times 100$

Angle of repose (Θ)

It is calculated by fixed funnel method. The values obtained for angle of repose of all formulations were tabulated in table no.3. The values were found to be in the range from 40˚.65′ and 53˚.50′ this indicate poor flow properties of powder. The angle of repose is determined by using following equation

$$\Theta = \tan^{-1} 2H/d$$

where H is height of funnel point , d is diameter of powder.

POST COMPRESSION STUDIES (R.Margret Chandira et al 2010 and B.Prakash Rao et al 2009)

Weight variation test- Randomly selected 20 tablets were weighed individually and together in a single pan balance. The average weight was noted and standard deviation was calculated. Every individual tablet in a batch should be in uniform weight and weight variation in within permissible limits.

Shape of the tablet

Microscopic examination of tablets showed circular shape, flat face with no cracks.

Diameter & Thickness

Control of physical dimensions of tablets such as thickness and diameter is essential for consumer acceptance and tablet uniformity. The thickness and diameter of tablets were measured in mm using Vernier Calipers. Randomly selected 5 tablets were subjected for test and average thickness and diameter was calculated.

Hardness test

Hardness of tablets was determined by diametric compression by using Monsanto type hardness tester. Randomly selected 5 tablets were subjected for hardness test and average hardness was calculated.

Friability test

The friability of tablets was measured in a Roche friabilator (Camp-bell electronics, mumbai), randomly selected 20 tablets were taken, initial weight (Wo) of 20 tablets was noted

then allowed for 100 revolutions in friabilator again taken the final weight (W) of 20 tablets. The percentage weight loss was calculated by –

$$F = \frac{Wo - W}{Wo} \times 100$$

In-Vitro Buoyancy Study

In-vitro buoyancy of each formulation was determined by floating lag time(FLT) and total floatation time (TFT). Tablet of each formulation were individually placed in a 200 ml beaker containing 0.1N HCl solution at 37± 0.5^{0C}. Time required for the tablet to rise to surface and float was FLT and the total time taken to remained buoyant without disintegration was TFT

In-Vitro Dissolution Studies

The release rate of Drotaverine HCl from the floating tablets was determined by using the USP type II dissolution test apparatus (paddle type). The dissolution test was performed using 1000 ml of 0.1N HCl at 37± 0.5^{0C} and 75 rpm. Ten-milliliter aliquots were withdrawn at time interval of 30 min, 1h, 2h, 4h, 6h, 8h, 12h, 16h, 20h and 24h. The samples were replaced by their equivalent volume of 0.1N HCl to maintain sink condition. The samples were analyzed at 361nm by UV spectrophotometer (UV-1700 pharmaspec, SHIMADZU). The percentage drug release was plotted against time to determine the release profile. The plot of cumulative percentage drug release versus time (hr) was plotted and depicted as shown in figure 1,2 and 3.

Drug Content Estimation

The drug content in each formulation was determined by triturating 20 tablets and powder equivalent to average weight was added in 100 ml of 0.1 N hydrochloric acid, followed by stirring 30 minutes. The solution was filtered through a 0.45µ membrane filter, diluted suitably and the absorbance of resultant solution was measured by spectrophotometer (UV-1700 pharmaspec, SHIMADZU) at 361 nm using 0.1 N hydrochloric acid as blank.

Process Optimization

Formulation of optimized batch F9 has been taken for the study of process parameters, the result showed that all optimized parameter were precise and they showed good results cumulatively in comparison to other formulation (F1 to F8).

ISSN: 0975-8585

Table 3: PRE COMPRESSION STUDIES

Code	Bulk density (gm/cm3)	Tapped density (gm/cm3)	Hausner ratio (HR)	Carr index (%)	Angle of repose
F1	3.804	5.737	1.508	33.69	44˚.49′
F2	3.888	6.140	1.579	36.67	46˚.50′
F3	3.723	5.833	1.566	36.17	40˚.65′
F4	4.117	6.363	1.545	35.29	41˚.29′
F5	3.645	5.384	1.477	32.29	45˚.73′
F6	3.977	5.645	1.419	29.54	47˚.90′
F7	3.846	5.223	1.358	26.36	53˚.50′
F8	4.022	5.384	1.338	25.29	52.64
F9	3.030	5.263	1.736	42.42	52˚.07′

Table 4: POST COMPRESSION STUDIES

Code	Weight variation (mg)	Diameter (mm)	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)
F1	439.36±0.189	11	5.4±0.135	5.8±0.144	0.59
F2	456.45±0.365	11	5.7±0.172	6.0±0.237	0.51
F3	472.32±0.172	11	5.8±0.217	6.0±0.291	0.56
F4	453.76±0.245	11	5.2±0.322	6.2±0.172	0.47
F5	486.25±0.212	11	5.5±0.137	5.4±0.129	0.54
F6	484.12±0.323	11	5.6±0.182	6.8±0.173	0.44
F7	470.68±0.133	11	5.4±0.155	5.5±0.199	0.60
F8	486.85±0.147	11	5.6±0.212	6.0±0.247	0.53
F9	501.20±0.266	11	5.8±0.111	6.4±0.135	0.48

Table 5

Code	Drug content (%)	Buoyancy Lag Time (sec.)	Total Floating Time (hrs)
F1	100.20	12	>24
F2	98.86	10	>24
F3	102.44	08	>24
F4	99.12	10	>24
F5	97.54	09	>24
F6	98.90	09	>24
F7	99.67	06	>24
F8	98.38	05	>24
F9	101.45	06	>24

ISSN: 0975-8585

Table 6: *In vitro* release profile of drotaverine HCl

%Cumulative drug release at	F1	F2	F3	F4	F5	F6	F7	F8	F9
30min	22.45	20.86	23.66	18.50	17.11	20.40	16.72	18.90	17.27
1h	31.33	27.56	32.28	24.76	24.30	25.25	22.57	25.55	23.65
2h	38.67	37.47	39.43	30.54	32.56	31.45	30.10	32.47	29.90
4h	47.55	48.25	46.21	36.66	40.65	39.34	38.87	42.81	37.48
6h	59.76	57.89	55.78	43.57	48.80	50.18	47.65	53.64	44.85
8h	68.22	66.34	67.88	54.90	57.10	62.53	56.44	64.17	52.44
12h	73.89	70.86	74.59	62.57	65.78	73.98	61.35	75.34	63.18
16h	80.45	79.33	83.73	70.24	72.60	80.10	78.80	83.67	74.50
20h	84.67	82.90	88.23	79.10	81.75	86.40	89.38	92.37	87.66
24h	87.44	88.58	91.40	86.64	88.20	93.56	92.70	95.33	98.74

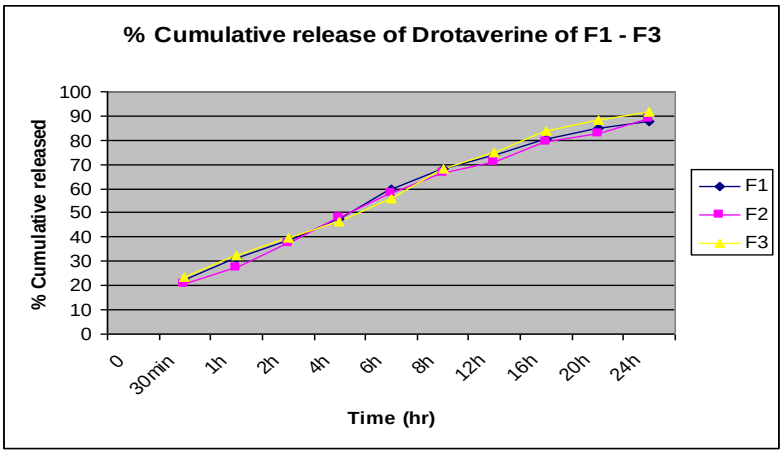


Figure 1: *In vitro* release profile of formulation (F1-F3)

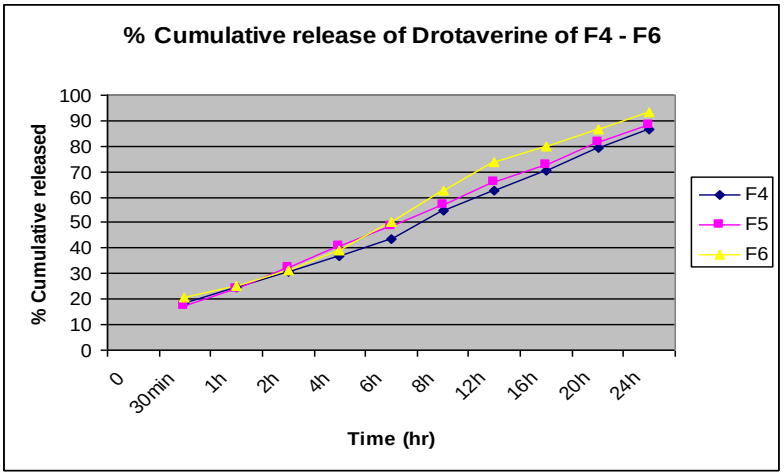


Figure 2: *In vitro* release profile of formulation (F4-F6)

ISSN: 0975-8585

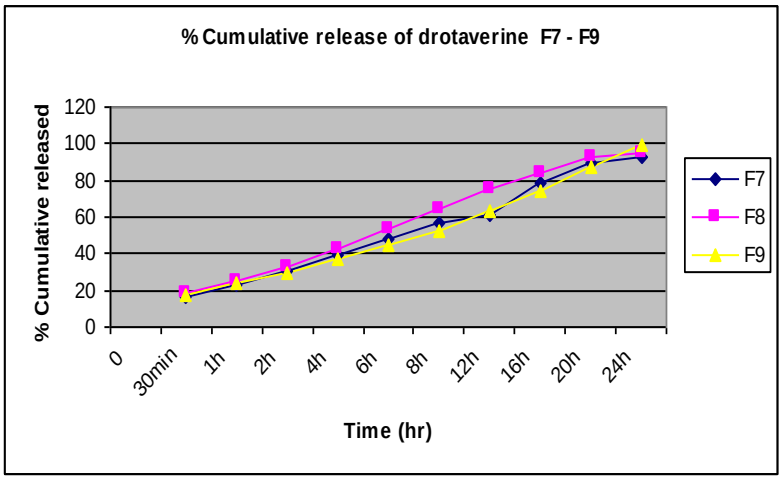


Figure 3: *In vitro* release profile of formulation (F7-F9)

RESULTS AND DISCUSSION

The powder thoroughly mixed with all ingredients are subjected to pre compression studies that the Hausner ratio (HR) varied between1.338 and1.736, Carr index varied between 25.29% and 42.42% and angle of repose is varied between 40˚.65′ and 53˚.50′ which shows the poor flow property of powder, therefore wet granulation method was adopted for granulation. The assayed content of drug in various formulations varied between 97.54% and102.44% .Tablet buoyancy lag time varied between 05 sec and 12 sec, where as total floatation of each formulation is greater than 24h. The combination of hydrophilic (HPMC) and hydrophobic (carbopol-934P) polymer provides a better option for 24h release action. The physical parameters hardness varied between 5.4 Kg/cm^{2}and 6.8 Kg/cm^2 and friability varied between 0.44% and 0.60%. The optimized formula F9 shows the constant release of drug for 24h and cumulative release of drug was 98.74%.

SUMMARY AND CONCLUSION

Drug bioavailability of Oral controlled drug delivery is influenced by various factors, a prolong gastric residence time (GRT), have been a topic of interest in terms of their potential for controlled drug delivery. 3^2 factorial design was employed containing 2 factors evaluated at 3 levels and the experimental trials were performed at all possible 9 combinations. Formulation of optimized batch F9 has been taken for the study of process parameters which shows the constant release of drug for 24h and cumulative release of drug was 98.74%.

ACKNOWLEDGEMENT

The authors wish to thank, Aurochem Pharmaceuticals (I) Pvt Ltd. Mumbai -India, for providing gift sample of Drotaverine HCl.

ISSN: 0975-8585

REFERENCES

[1] Punna RR. Design and in vivo evaluation of Zidovudine oral controlled release tablets prepared using hydroxy propyl methylcellulose. Chem pharm bull 2008; 56(4); 518-524.

[2] Dalavi VV, Patil JS. Gastroretentive drug delivery system of an antiretroviral agent. Int J of pharm Tech res 2009; 1:1678-1684.

[3] Singh KC, Jain P. Drotaverine HCl for augmentation of labour. Int J Gynaeco Obstet 2004; 84(1):17-22.

[4] Drach GW. Urinary lithiasis, etiology, diagnosis, and medical management of acute stone episodes. In Walsh PC, Rtik AB, Stamey TA, Vaughan ED J reds, Campbell's urology, 6th edition 1998; 2101-2112.

[5] Tripathi KD. Essential medical pharmacology, 5th edition, Jaypee prakashan, 2004, 419-20.

[6] R Margret Chandira, Debjit Bhowmik, Chiranjib, B Jayakar. Formulation and Evaluation of gastroretentive drug delivery system of gastroprokinetic drug Itopride hydrochloride. Int j of pharmacy and Pharmaceutical sci 2010; 2: 53-65.

[7] B Prakash Rao, Neelima Ashok Kottan, Snehith VS Ramesh C. Development of Gastro retentive drug delivery system of cephalexin by using factorial design. ARS Pharmaceutics 2009; 50: 8-24.

[8] L Whitehead, JT Collett, HL Sharma, AM Smith. Floating dosage forms: an in vivo study demonstrating prolonged gsstric retention. J of controlled relase 1998; 55: 3-12.

[9] Monica RP Rao, Girish S Sonar, Rachana R Mandsauwale. Evaluation of floating matrix tablet formulation of salbutamol sulfate using full factorial design. Asian J of pharmaceutics 2009; 43-49.

[10] Ravi Kumar, MB Patil, Sachin R patil, Mahesh s Paschapur. Formulation and evaluation of effervescent floating tablet of Famotidine. Int J of pharm tech research 2009; 3: 754-763.

[11] S Sarojini, D Arivazagan, R Manavalan, V Jaynthi. Buoyant sustained release tablets based on polyethylene oxide. Int J of pharmacy and pharmaceutical sciences 2010; 2(1): 144-149.

[12] Kapui Z. Summary of the specific pharmacological studies of drotaverine HCl (NO-SPA). The management of smooth muscle spasm. Special monograph. Budapest: Pap A, 1998; 45-89.

[13] Vargay Z. Summary of the pharmacokinetic and metabolism studies of drotaverine (NO-SPA. Therapia Hungarica 1989; 89:21-29.

[14] Shashikant D, Barhate, Dr Madhabhai M Patel, Amol b Patil. Formulation and optimization of controlled released floating tablets of clarithromycin. J of pharmacy research 2009; 2: 445-448.

[15] RO Grey and JK Beddow. On the Hausner Ratio and its relationship to some properties of metal powders. Powder Technology 1969; 2(6): 323-326.

[16] Q Li. Interparticle van der Waals force in powder flowability and compactibility. Int J of Pharmaceutics. 2004; 280 (1-2): 77-93.

[17] C Conesa. Characterization of Flow Properties of Powder Coatings Used in the Automotive Industry. Kona 2004; 22: 94-106.