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Development and Optimization of Gastro-Retentive Formulation of Hydralazine HCl

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ABSTRACT

Hydralazine hydrochloride has a half-life of 2 to 4 hours with an oral bioavailability of 26-50%. Since hydralazine has a demethylating effect on various suppressor genes, it can be used in various types of cancer to support chemotherapy. The purpose of this study was to optimize and evaluate floating tablets of hydralazine hydrochloride designed to prolong the gastric residence time and to provide controlled release of the drug for 24 h. The floating tablets of hydralazine hydrochloride were prepared by the wet granulation method. Polymers of hydroxy propyl methyl cellulose (HPMC K100M), HPMC K15M, carbopol 940 and sodium bicarbonate were used as the release retarding agents. This study investigated utility of a 3-factor, 3-level Box-Behnken design and optimization process for floating tablet of Hydralazine with 5 replicates of center points. Amount of HPMC K4 (Hydroxy Propyl Methyl cellulose), amount of sodium bicarbonate were selected as the independent variables whereas total floating time (TFT), T90, % cumulative drug release at 24 hours, and T20, Q1 were selected as dependent variables. Non-Fickian diffusion release transport was confirmed as the release mechanism for the optimized formulation and the predicted values agreed well with the experimental values. Drug excipient compatibility studies were investigated by FTIR, DSC and XRD. The produced tablets exhibited good floating time and controlled drug release over a period of 24 h. The resultant data were critically analyzed to locate the composition of optimum formulations. All predicted values of response variables of optimized formulation demonstrated close agreement with the experimental data during optimization procedure.

Keywords: Hydralazine, Floating oral dose, Box-Behnken, HPMC K4M, Carbopol 940, Sodium bicarbonate.

INTRODUCTION

Globally, more than 43 million people are infected with the Hypertension syndrome Hypertension (HTN) or high blood pressure, sometimes called arterial hypertension, is a chronic medical condition in which the blood pressure in the arteries is elevated. Hypertension is classified as either primary (essential) hypertension or secondary hypertension; about 90–95% of cases are categorized as "primary hypertension" which means high blood pressure with no obvious underlying medical cause. The remaining 5–10% of cases (secondary hypertension) is caused by other conditions that affect the kidneys, arteries, heart or endocrine system. Vasodilators that act primarily on resistance vessels (arterial dilators) are used for hypertension and heart failure, but not for angina because of reflex cardiac stimulation.

The gastro retentive drug delivery systems can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the gastrointestinal tract. These systems help in continuously releasing the

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drug before it reaches the absorption window, thus ensuring optimal bioavailability. Local delivery also increases the stomach wall receptor site bioavailability and increases efficacy of drugs to reduce acid secretion. Hence this principle may be applied for improving systemic as well as local delivery of Hydralazine, which would efficiently reduced gastric acid secretion. [1-3]

Various approaches including floating systems, mucoadhesive systems, conventional system and in situ gel systems have been successfully employed to improve the gastric residence time of a delivery system. Though highly efficient for gastro retention, floating systems suffer from a major disadvantage that they are effective only when the fluid level in the stomach is sufficiently high. However, as the stomach empties and the tablet is at the pylorus, the buoyancy of the dosage form may be impeded. This serious limitation can be overcome by making the system eventually adhere to the mucous lining of the stomach wall. Mucoadhesion along with floating system has been an extensively adapted approach for achieving site-specific drug delivery through the amalgamation of mucoadhesive polymers within pharmaceutical formulations along with the active pharmaceutical ingredient (API). Mucoadhesive materials are hydrophilic macromolecules containing numerous hydrogen bond forming groups. The mechanism by which mucoadhesion takes place has been said to be in two stages: the contact (wetting) stage followed by the consolidation stage (establishment of adhesive interactions). The objective of the current study was to develop floating-mucoadhesive tablets of Hydralazine hydrochloride and optimize their mucoadhesive and drug release characteristics using the benefits of BoxBehnken design methodology.

MATERIAL AND METHODS

The Active pharmaceutical ingredient was procured from Sun Pharma Ltd, Vadodara, India and was British Pharmacopeia grade. The excipients were gifted by SD fine chemical, Vadodara, India and were United Pharmacopeia grade. Melting points of Active pharmaceutical ingredient were determined in open capillaries using Veego melting point apparatus, Model VMP-D (Veego India Ltd., Mumbai, India) and were uncorrected. Infrared spectra were recorded using KBr pellets on SHIMADZU-FT-IR 8400S instrument. Mass spectra were recorded on PerkinElmer LC–MS PE Sciex API/65 Spectrophotometer. The ^{1}H NMR spectra were recorded on Brucker Avance-300 (300 MHz) model spectrophotometer in $CDCl_3$ using DMSO as solvent. SHIMADZU dissolution apparatus was used to study drug release profile. Pfizer tester was used for hardness evaluation. Satorious LOD instrument for measuring Loss on drying (LOD).

Various methods and characterization of the Formulations are reported as below.

Floating Systems [4]

a. Effervescent floating dosage forms
b. Non effervescent dosage forms.
c. Raft forming systems.

Floating systems or hydro dynamically controlled system are low density system that has sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for the prolong period of time. [5] While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the systems. After release of the drug, the residual system is emptied from the stomach. This result in increased GRT and a better control of the fluctuation in the plasma drug concentration.

Effervescent floating dosage forms [6]

These are matrix type of system prepared with the help of Swellable polymers such as methyl cellulose and chitosan and various effervescent compounds, examples; sodium bicarbonate, tartaric acid and citric acid. They are formulated in such a way that when in contact with acidic gastric contents, CO_2 is liberated and get entrapped in swollen hydrocolloids, which provides buoyancy to the dosage form.

Non Effervescent Floating Dosage Forms

Non effervescent floating dosage form use a gel forming or swellable cellulose type hydro colloids, polysaccharides and matrix forming polymer like poly carbonate, polyacrylate, polymethacrylate, polystyrene. The formulation method includes a simple approach of thoroughly mixing the drug and gel forming hydro colloid. After oral administration, this dosage form swells in contact with gastric fluids attains a bulk density. The air entrapped within the swollen matrix imparts buoyancy to the dosage form. The so formed swollen gel-like structure acts as a reservoir and allows sustained release of the drug through the gelatinous mass.

Raft Forming Systems

Here, a gel forming solution (example Sodium alginate solution containing carbonates or bicarbonates) swells and forms a viscous cohesive gel containing entrapped CO_2 bubbles in contact with gastric fluid. Formulations also typically contain antacids such as aluminum hydroxide or calcium carbonate to reduce gastric acidity. Because raft-forming systems produce a layer on the top of gastric fluids, they are often used for gastroesophaeal reflux treatment as with liquid.

Mucoadhesive or bioadhesive systems

The basis of mucoadhesion is that a dosage form can stick to mucosal surface by different mechanisms. Different theories are invoked to explain these mechanisms. The wetting theory is based on the ability of bioadhesive polymers to spread and develop intimate contact with mucus layers and finally, the diffusion theory proposes physical entanglement of mucin strands and the flexible polymer chains, or an interpenetration of mucin strands into the porous structure of polymer substrate.

Table 1: List of drug and excipients

Materials	Company
Hydralazine	Sun Pharma ltd, Vadodara
Starch	S D Fine Chem, Mumbai
Sodium Bicarbonate	S D Fine Chem, Mumbai
Sodium Alginate	S D Fine Chem, Mumbai
HPMC K4M	S D Fine Chem, Mumbai
Carbopol 940P	S D Fine Chem, Mumbai
DCP	S D Fine Chem, Mumbai
MCC	S D Fine Chem, Mumbai
SSG	S D Fine Chem, Mumbai
Aerosil	S D Fine Chem, Mumbai
Talc	S D Fine Chem, Mumbai
Magnesium Stearate	S D Fine Chem, Mumbai

Table 2: List of drug excipients concentration for batch

Materials	Quantity
Hydralazine	50 mg
HPMC K4M	65 mg
Carbopol 940P	60 mg
Sodium Bicarbonate	30 mg
Starch	50 mg
Water	Q.S.
SSG	5 mg
Aerosil	5 mg
Talc	2.5 mg
Mg Stearate	2.5 mg
Tablet Weight	**270 mg**

Table 3: Results of evaluation parameter

Batch No	Tablet Thickness (mm)	Tablet Hardness (g/cm^3)	Average Weight (mg)	Tablet friability (%)	CCPR (%)
B1	2.41±0.05	1±0.01	270.5	0.63±0.01	98.0
B2	2.39±0.04	1±0.02	271	0.7±0.01	99.1
B3	2.40±0.04	1±0.01	270	0.69±0.02	99.6
B4	2.39±0.03	1±0.03	270	0.74±0.01	98.4
B5	2.39±0.04	2±0.01	268	0.7±0.01	98.0
B6	2.39±0.03	2±0.03	270	0.63±0.01	99.1
B7	2.40±0.04	2±0.01	270	0.69±0.02	99.8
B8	2.39±0.05	2±0.02	270	0.7±0.01	98.0
B9	2.39±0.04	1±0.03	271	0.63±0.01	99.3
B10	2.40±0.04	2±0.03	270	0.63±0.01	99.6
B11	2.41±0.03	2±0.03	269	0.74±0.01	99.1
B12	2.40±0.05	2±0.01	271	0.69±0.02	99.9
B13	2.39±0.04	1±0.03	270	0.74±0.01	98.0
B14	2.41±0.04	2±0.03	270	0.69±0.02	99.6
B15	2.41±0.05	2±0.02	271	0.63±0.01	99.9
B16	2.39±0.03	1±0.03	269	0.7±0.01	99.1
B17	2.40±0.05	2±0.01	270	0.74±0.01	98.0

Table 4: Accelerated stability study data

Parameters	Specification	1 Month	2 Month	3 Month	6 Months
Description	White to off white color tablets	Complies	Complies	Complies	Complies
Water content	NMT 0.5%	0.3%	0.3%	0.3%	0.3%
Assay (By HPLC)	Not less than 95-105%	98.5%	98.35 %	98.22 %	98.10 %

Formulation Method

Pure Hydralazine HCl and excipients were accurately weighed and were collected in a mortar and pestle. The mixture was well mixed in blender for 10 mins in order to achieve uniform mixing and was passed through sieve number 40. Remaining material was then passed through sieve number 20 in order to get uniform mixing. The blend was binded and dried up to desire LOD was obtained. This blend was compressed using 9.0mm S/C punches.

Table 5: Experimental design code values

Translation of coded values in actual units			
Independent variables	**Levels used, actual (coded)**		
	Low(-1)	**Medium (0)**	**High (+1)**
Concentration of HPMC K4M (%w/w) = X1	20	40	70
Concentration of Sodium Alginate (%w/w)=X2	5	10	15
Concentration of Carbopol 940P (%w/w) = X3	10	15	20

Dependent variables
Y1= Time required to release 90% of drug (t90 in hrs)
Y2= Time required to release 20% of drug (t20 in hrs)
Y3= Q1 (Amount of drug release in 1hr (%))

Table 6: Factorial design runs

Batches	X1	X2	X3	X12	X13	X23	X11	X22	X33
F1	1	0	-1	0	-1	0	1	0	1
F2	0	0	0	0	0	0	0	0	0
F3	0	-1	1	0	0	-1	0	1	1
F4	0	0	0	0	0	0	0	0	0
F5	0	1	1	0	0	1	0	1	1
F6	-1	0	1	0	-1	0	1	0	1
F7	-1	1	0	-1	0	0	1	1	0
F8	-1	0	-1	0	1	0	1	0	1
F9	0	0	0	0	0	0	0	0	0
F10	0	0	0	0	0	0	0	0	0
F11	0	1	-1	0	0	-1	0	1	1
F12	0	0	0	0	0	0	0	0	0
F13	1	0	1	0	1	0	1	0	1
F14	1	-1	0	-1	0	0	1	1	0
F15	0	-1	-1	0	0	1	0	1	1
F16	1	1	0	1	0	0	1	1	0
F17	-1	-1	0	1	0	0	1	1	0

Table 7: Optimized batches formulation table

Batch	API (mg)	HPMC K4M (mg)	Sodium Alginate (mg)	Carbopol 940P (mg)
O1	50	52.0	44.5	42.5
O2	50	52.5	45.0	43.0
		Tablet weight: 250mg		

RESULTS

All the batches for all dosage forms were formulated and evaluated on the same ground and best dosage form was selected and was compared with the optimized batches in order to get desired and reproducible results. While carrying out the experiment evaluation parameters like weight variation, content uniformity, thickness, hardness, friability test, floating lag time and *in-vitro* dissolution study were carried out and suitable results were then optimized using experiment design software.

15 trial runs with different concentrations were carried out and compared. The best trial batched giving desire results was short listed and compared with different dosage forms in order to select the best delivery system keeping in consideration all the parameters.

While comparing the dosage forms it was found that all the different dosage forms yield different results when measured under same ground. Based on the evaluation

it was found that floating delivery system yield the best desired and reproducible results.

Table 8: Evaluation of optimized batches

Batch No.	Tablet Thickness (mm)	Tablet Hardness (kg/cm3)	Drug content (%)	T90	T20	Q1	%CCPR (%)
O1	2.39	1-2	99.16	7 hr	6hr 45min	21.68	99.16
O2	2.41	1-2	99.66	6hr 10min	7hrs	20.00	99.96

Table 9: Comparison of final batch (B1) and optimized batch O1 & O2

Time (hrs)	Final Batch %CCPR	Optimized Batch	
	B1	O1	O2
1	1.21	1.54	1.99
3	3.11	4.12	3.14
5	8.1	8.9	9.7
8	15.86	16.55	15.43
12	24.99	25.18	28.17
16	42.98	39.12	43.91
20	61.55	59.44	60.64
22	78.56	80.39	79.87
24	99.89	99.48	99.97

Table 10: Comparison of Floating Tablets (FLT), Mucoadhesive Tablets (MA), In-situ gel (SG), Conventional Tablets (CT)

Time (hrs)	FLT	MA	SG	CT
1	1.21	3.11	12.56	10.78
3	3.11	9.23	45.98	32.07
5	8.1	13.12	74.18	64.1
8	15.86	16.55	98.32	86.99
12	24.99	25.18	99.12	99.1
16	42.98	39.12	99.2	99.32
20	61.55	98.18	99.2	99.32
22	78.56	98.77	99.2	99.32
24	99.89	99	99.2	99.32

The stability studies *viz* accelerated and real time were carried out for all the trial and it was found the all the batches which were formulated were found to be stable and their physio-chemical properties were unchanged. The stability batches were subjected to calculate the drug release profile and it was found that the profile was same as that was before. This formula was optimized [7-9] using experimental design software by keeping in consideration dependent and independent variables. The 3D contour plot was obtained and was interpreted. [10-13]

Formulation Design (BOX-BEHNKEN DESIGN) [14-16]

A 3-factor 3-level Box-Behnken design was used for the formulation of tablets. This design is suitable for exploring quadratic response surface and constructing second order polynomial models. The design consists of replicated center points and the set of points lying at the midpoint of the multidimensional cube that defines the region of interest. The non linear quadratic model generated by the design in the form:

$$Y = X0 + X1A + X2B + X3C + X4A2 + X5B2 + X6C2 + X7AB + X8BC + X9AC + E$$

Where, Y is the measure response associated with each factor level combination: X0 is an intercept: X1 - X9 are the regression coefficient: A, B, C are the factor studied and E is the associated error term.

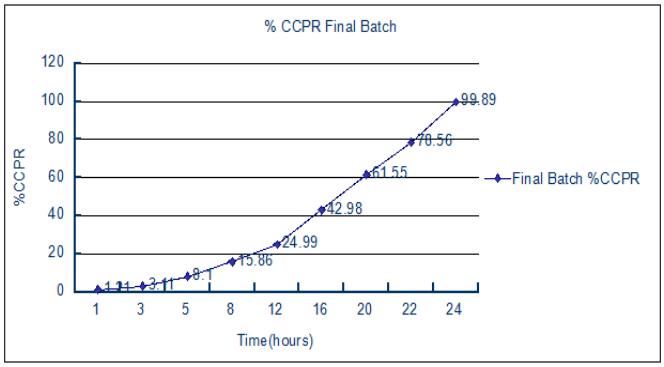

Fig. 1: %CCPR of final batch (B1)

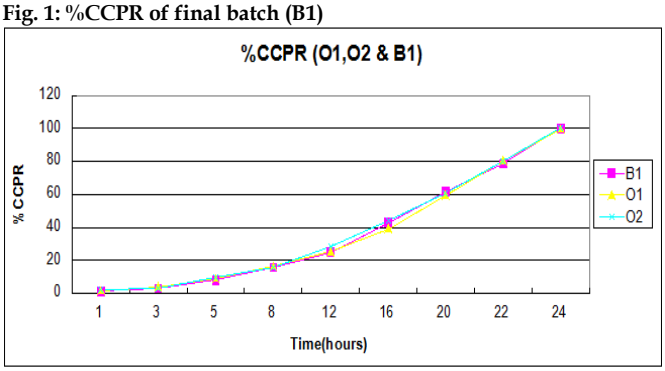

Fig. 2: Comparison of final batch (B1) with optimized batch (O1 & O2)

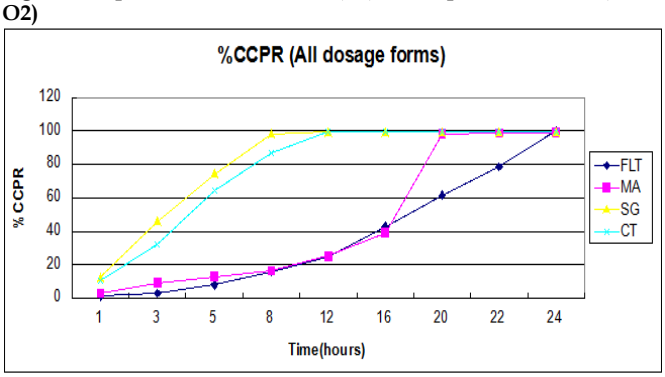

Fig. 3: Comparison of Floating Tablets (FLT), Mucoadhesive Tablets (MA), In-situ gel (SG), Conventional Tablets (CT)

DISCUSSION

All the batches were formulated keeping in consideration each and every critical parameters and the trial runs were formulated in order to adjust the concentration which yield to desired results. In order to know which is the best delivery system four different dosage forms were formulated and it was found that floating dosage form yield the best results followed by floating muco-adhesive tablets. All the batches were optimized using experimental design software by keeping in consideration dependent and independent variables. By using the Experimental design software two optimized batches were formulated keeping in consideration the desired results. Later the final batch was prepared and compared with optimized batches and it was observed that floating effervescent dosage form was found satisfactory and all the aim for the research was achieved.

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