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Formulation and Evaluation of Verapamil HCL Gastroretentive Floating Tablet from matrices prepared using Compritol ATO 888.

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ABSTRACT

The purpose of this investigation was to prepare a gastroretentive drug delivery system of Verapamil HCL. Floating tablets of Verapamil HCL were prepared employing solid dispersion technique with compritol-888ATO. By using different release enhancer like Lactose, Microcrystaline cellulose & HPMC K 100 LV. Cetyl alcohol was incorporated as a lower density agent. The floating tablets were evaluated for uniformity of weight, hardness, friability, drug content, *in vitro* buoyancy and dissolution studies. The effect of release enhancer on drug release profile and floating properties was investigated. The prepared tablets exhibited satisfactory physico-chemical characteristics. Formulation containg Lactose & HPMC k 100 LV showed good *in vitro* buoyancy but Formulation containg Microcrystalline cellulose Failed to float. Increase in the Cetyl alcohol level Increase the floating time but it affect integrity of tablets. The drug release from the tablets was sufficiently sustained and Fickian transport of the drug from tablets was confirmed. The fabricated floating tablet formulations were subjected for stability study at 40^0C and relative humidity at 75 % for three months. The product was evaluated for, buoyancy, drug content and *in vitro* dissolution test. After stability study drug release increased slightly but there is no change in physical appearance.

Keywords: Verapamil HCL, floating tablets, *in vitro* buoyancy.

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INTRODUCTION

Verapamil HCL has been shown to be effective and safe alone or in combination, in patients with hypertension and/or coronary artery diseases .The profile of Verapamil hydrochloride indicates that it is a drug with short half-life (4-6 hrs.) and hence requires frequent dosing, like 3-4 tablets daily (dose 40mg)[1]. These frequent dosing results in fluctuating drug levels in body and need for constant monitoring and counseling of patient for adherence to dose regimen. Verapamil hydrochloride shows high solubility in acidic pH of stomach (pH 1-3) than relatively high pH of small intestine (pH 4-6). This fact may therefore support faster absorption of drug in stomach with higher concentrations entering in plasma and hence improving its bioavailability. Thus, to develop floating drug delivery system for Verapamil hydrochloride is clearly justified. Verapamil hydrochloride is high soluble in stomach, when prolong release of soluble drug is required water insoluble or hydrophobic polymer must be required [2].

The gastroretentive 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 drug before it reaches the absorption window, thus ensuring optimal bioavailability by using release enhancer in controlled or sustained release formulations[3], diffusion, swelling and erosion are the three most important rate controlling mechanisms followed. The drug release from the polymeric system is mostly by diffusion, swelling and is best described by Fickian diffusion [4]. In the present investigation floating tablets of Verapamil hydrochloride were prepared by low density approach using three different grades of release enhancer with drug-complex. The aim of the work was to evaluate the effect of polymer floating properties and release characteristics of Verapamil hydrochloride tablets [5].

MATERIALS AND METHODS

Materials

Verapamil hydrochloride was received as a gift sample from Cipla Limited, Patalganga, India. Compritol-888 ATO & HPMC K 100 LV was received as gift samples from Colorcon Asia Pvt. Ltd. Goa, India. Microcrystalline cellulose, Magnesium stearate, was purchased from S.D. Fine-Chem Ltd, Ahmedabad, India. Lactose was purchased from E. Merck (India) Ltd., Mumbai. All other ingredients were of laboratory grade.

Method

FTIR Studies

The IR spectra of previously dried samples of drug and excipients were recorded by potassium bromide dispersion technique. 2-3 mg of sample of polymer was mixed with

previously dried potassium bromide and kept in sample cell, the cell was then fitted on sample holder and IR spectra were recorded using FTIR instrument with diffused reflectance.

Preparation of solid dispersion by hot fusion method

Composition of solid dispersion (shown in Table No-1).The matrices were prepared by hot fusion method where the lipids were melted with continuous stirring in a porcelain dish placed on a water bath maintained at approximately 70° c. Verapamil HCL was added to the fused lipid (Compritol-888 ATO) with continuous stirring, with addition of release enhancer. The weight ratio of drug to the lipophillic excipients was 1:2(w/w).In order to study the effect of Different ratio of lactose, MCC and HPMC K 100 LV on the release of the drug from the tablet with the matrices, solid dispersion are prepared with the addition of such release enhancer. The molten mass of each formulation are allow cooling down and screened through 60-mesh sieve. The samples were stored in a desiccator at room temperature until use.

Preparation of floating matrix tablets by direct compression method

Solid dispersion was obtained from hot fusion method was mixed with cetyl alcohol as a low density diluents, with addition of 1% Magnesium stearate as a lubricant. (Shown in Table No-2)This blend was mixed properly for 2 minute. The blend was directly compressed using 10-station rotary tablet machine (Clit Pilot Press) fitted with 12mm Diameter normal flat surface punches and die sets. Relatively constant tablet hardness was held around 4kg for compression. The tablet having luminous surface, were stored in plastic container until use.

Evaluation of solid dispersion

The flow properties of solid dispersion (before compression) were characterized in terms of angle of repose, Carr index and Bulk density. For determination of angle of repose (θ), the solid dispersion 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 2.0cm above hard surface. The granules were poured till the time when upper tip of the pile surface touched the lower tip of the funnel. The $\tan^{-1}$ of the (height of the pile / radius of its base) gave the angle of repose. Granules were poured gently through a glass funnel in to a graduated cylinder cut exactly to 10 ml mark. Excess solid dispersion was removed using a spatula and the weight of the cylinder with pellets required for filling the cylinder volume was calculated. The cylinder was then tapped from a height of 2.0cm until the time when there was no more decrease in the volume. Bulk density (ρb) and tapped density (ρt) were calculated. Carr indexes (IC) were calculated according to the two equations given below [6]:

$IC = (\rho t - \rho b)/\rho t$

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Evaluation of Floating Tablets:

The prepared floating tablets were evaluated for Thickness [7], hardness (Monsanto tester), friability using 10 tablets (Roche type friabilator), drug content [8], Density, *in vitro* buoyancy and *in vitro* dissolution studies [9]. The results are expressed as mean ± S.D. (n=5). The tablets were placed in a 100 ml beaker containing 0.1N hydrochloric acid. The duration of time the dosage form constantly remained on the surface of medium was determined as the total floating time. The drug content in each formulation was determined by triturating 20 tablets and powder equivalent to average weight was added in 100ml of 0.1N hydrochloric acid, followed by stirring for 30 minutes. The solution was filtered through a 0.45µ membrane filter, diluted suitably and the absorbance of resultant solution was measured spectrophotometrically at 278 nm using 0.1 N Hydrochloric acid as blank. The release rate of Verapamil HCL from floating tablets was determined using *United States Pharmacopeia* (USP) Dissolution Testing Apparatus 2 (paddle method; Veego Scientific, Mumbai, India). The dissolution test was performed using 900 ml of 0.1N hydrochloric acid, at 37 ± 0.5°C and100 rpm. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus hourly and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45µ membrane filter and diluted to a suitable concentration with 0.1N hydrochloric acid. Absorbance of these solutions was measured at 278nm using a Shimadzu 1800UV/Vis double-beam spectrophotometer. Cumulative percentage drug release was calculated using an equation obtained from a standard curve.

Stability studies

Stability is the essential factor for quality, efficacy and safety of drug product. The drug product with insufficient stability can result in change of their physical (hardness, dissolution rate, phase separation) as well as chemical characteristics (formation of high risk decomposition substances). Present study was carried out to check the dissolution behavior and physical appearance of optimized batch. The batch was selected as an optimum batch depending upon release rate and floating properties and the stability study was carried out at accelerated conditions of 40 °C / 75%RH Condition for period of three months.

RESULT AND DISCUSSION

FTIR Study

IR spectrum of Verapamil hydrochloride. It shows characteristic peaks of aromatic C-H stretching and N-H stretching at 3250 cm-1 and 3400 cm^{-1} respectively. The IR spectra of all the matrix forming polymers clearly revealed the presence of peaks associated with functional groups C=O, -OH, aliphatic C-H. This further supports the chemical identity of these polymers. Analysis of IR spectra of solid dispersions of Verapamil hydrochloride with Compritol revealed the decrease in intensity of characteristic peaks of aromatic C-H stretching of methyl and methylene groups (3030 and 2860 cm^{-1}), C-O stretch in methoxy group while the broad peak for

the N-H stretch remained unchanged. These results thus indicate that there is no probable chemical interaction between drug and carrier when formed as solid dispersion. (See fig No-1).

Flow Properties of solid dispersion

The solid dispersion prepared for compression of floating tablets was evaluated for their flow properties (Shown in Table No- 3). Angle of repose was in the range of 15.25 to 17.51 with solid dispersion of different formulation. Loose bulk density ranged between 0.3879 to 0.4685 gm/cm^3 and Tapped density ranged between 0.8737 to 0.4613gmcm3. Carr index was found to be 14.81to 20. These values indicate that the prepared granules exhibited good flow properties.

Evaluation of Floating Tablets

The floating tablets of Verapamil HCL were prepared by low density powder cetyl alcohol and matrix forming polymer. Magnesium stearate was used as lubricant. The results of the physico-chemical characterization are (shown in Table No- 4).

The thickness of the tablet varied between 2.5 mm to 2.6 mm for different formulations with low standard deviation values. The variation in weight was within the range of ±5% complying with pharmacopoeia specifications. The hardness for different formulations was found to be between 3.6 to 4.2 kg/ cm^2 indicating satisfactory mechanical strength. The friability was below 1% for all the formulations, which is an indication of good mechanical resistance of the tablet. The drug content varied between 95.99 to 98.56mg in different formulations with low coefficient of variation (C.V. < 1.0%), indicating content uniformity in the prepared batches. Density of tablet was found to be in the range of 1.05 to 1.15 which is lower than gastric fluid. To float remain of the medium up to more than 12 hrs. Formulations containing CL1,CL2,CW1 and CW2 were float up to 12 hrs, but formulation containing MCC as release enhancer did show satisfactory buoyancy but lost the mechanical strength(after 2 hrs). This may attributed to disaggregation of matrix component due to pressure exerted by swollen mass resulting disintegration of tablet.

It is evident from the *in vitro* dissolution data that increases concentration of release enhancer increases the release rate but reduced the floating time. In case of low density powder, concentration increases integrity of the tablet decreases. The drug release from floating tablet containing lactose as a release enhancer was found to be 40.05 and 57.93 for CL1 and CL2. In this case of dissolution of tablet lactose radialy dissolve and diffuse out of matrix thus leaving channels or pores in matrix structure from this drug leach out from solid dispersion.

The drug release Formulation Containing HPMC K100 LV as a release enhancer was found to be 53.27 and 65.17 for CW1 and CW2. In this formulation release is done by minimal swelling and mainly by erosion mechanism [10]. In all above formulation CW2 shows better-sustained release characteristics with excellent *in vitro* buoyancy (Fig No-2).

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The data obtained from *in vitro* dissolution studies were fitted in different models viz. zero order, first order, Highuchi and Korsemeyer's equation. To confirm the exact mechanism of drug release from these tablets Regression analysis was performed and regression values 'r2' were 0.9944 for Optimized formulations. The 'n' value for selected floating formulation was less than 0.5, indicating the drug release mechanism to be matrix diffusion. The model of the drug release followed was Higuchi [11].The diffusion mechanism can change from pure Fickian to anomalous transport and the drug release can approach the first order from Highuchi kinetics.

Stability study

The result of accelerated stability studies carried out according to ICH guidelines. There was no any change in physical appearance in the dosage form over a period of three months in accelerated conditions (40°C / 75 %RH).There is no change floating time and drug content of the formulation. The drug release from experimental floating matrix stored at ambient environmental conditions was slightly higher than the studied previously. This may be attributed to the transition of initial partially amorphous structure of lipids which gradually crystallise with time. The rate of crystallization was reported to be dependent on the ageing. The aging involves changes in physical structure and chemical composition during storage. The increase in release may be attributed to the development of surface cracks caused by phase transformation during aging [12].

Table No-1 Composition of solid dispersion of Verapamil hydrochloride with Compritol containing release enhancer

Ingredients	Quantities (mg)		
Verapamil Hydrochloride	120	120	120
Compritol-888 ATO	100	100	100
Lactose/ Microcrystalline cellulose/ HPMC K100 LV	10	20	30
Total weight	230	240	250

CONCLUSION

In conclusion a single unit, floating drug delivery system has been developed, which is based on low density powder and matrix-forming polymer(s). Its in vitro floating performance and the ability to control drug release over prolonged periods of times have been demonstrated. The drug release patterns can effectively be adjusted by varying simple formulation parameters, such as the "matrix-forming polymer /low density powder" ratio, initial drug loading, tablet thickness and diameter, type of matrix forming polymer, addition of water-soluble and water in-soluble fillers, and the use of polymer blends. Thus, desired release profile adapted to the pharmacokinetics/pharmacodynamic properties of the incorporated drug can easily be provided.

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Table No-2 Formulation containing release enhancer for Verapamil hydrochloride –compritol solid dispersion system.

Ingredients (mg per tablet)	Role	CL1	CL2	CL3	CM1	CM2	CM3	CW1	CW2	CW3
Solid dispersion of Verapamil Hydrochloride containing release enhancer	Matrix system containing drug	230	240	250	230	240	250	230	240	250
Cetyl alcohol	Low density diluent	80	80	80	80	80	80	80	80	80
Magnesium Stearate	Lubricant	2.6	2.8	3	2.6	2.8	3	2.6	2.8	3
Total weight of matrix tablet		310	320	330	310	320	330	310	320	330

Table no-3 Flow Properties of solid Dispersions

Code	Angle of repose	Loose bulk density (LBD)	Tapped bulk density (TBD)	Carr's index
CL1	16.28±0.05	0.4685	0.5511	15
CL2	17.51±0.03	0.4420	0.5261	16
CL3	15.25±0.03	0.3879	0.4613	15.90
CM1	14.34±0.02	0.4078	0.5516	17
CM2	15.89±0.05	0.3919	0.4657	15.78
CM3	16.03±0.04	0.4570	0.8567	16
CW1	16.36±0.04	0.4091	0.4910	16.66
CW2	15.28±0.06	0.4035	0.4736	14.81
CW3	16.24±0.02	0.4699	0.8737	20

Table No-4 Data for evaluation of floating matrix tablets

Code	Drug content (%)	Hardness (Kg/cm^2)	Thickness (mm) (±SD)	Density g/cm^3	Duration of floating
CL1	95.99	3.7	2.5±0.031	1.05 ±0.02	> 8hrs
CL2	98.56	3.6	2.5 ±0.02	1.05 ±0.01	> 8hrs
CL3	97.22	4.1	2.6±.03	1.12±0.10	Up to 6 hrs
CM1	97.19	3.7	2.5±0.031	1.15 ±0.02	-----
CM2	98.16	3.6	2.5 ±0.02	1.13 ±0.01	-----

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CM3	98.32	4.2	2.6±0.04	1.14±0.07	-----
CW1	98.1	3.8	2.5±0.02	1.07±0.02	> 8hrs
CW2	97.6	3.8	2.5±0.014	1.07±0.01	> 8hrs
CW3	97.10	3.8	2.5±0.02	1.05 ±0.02	Up to 4 hrs

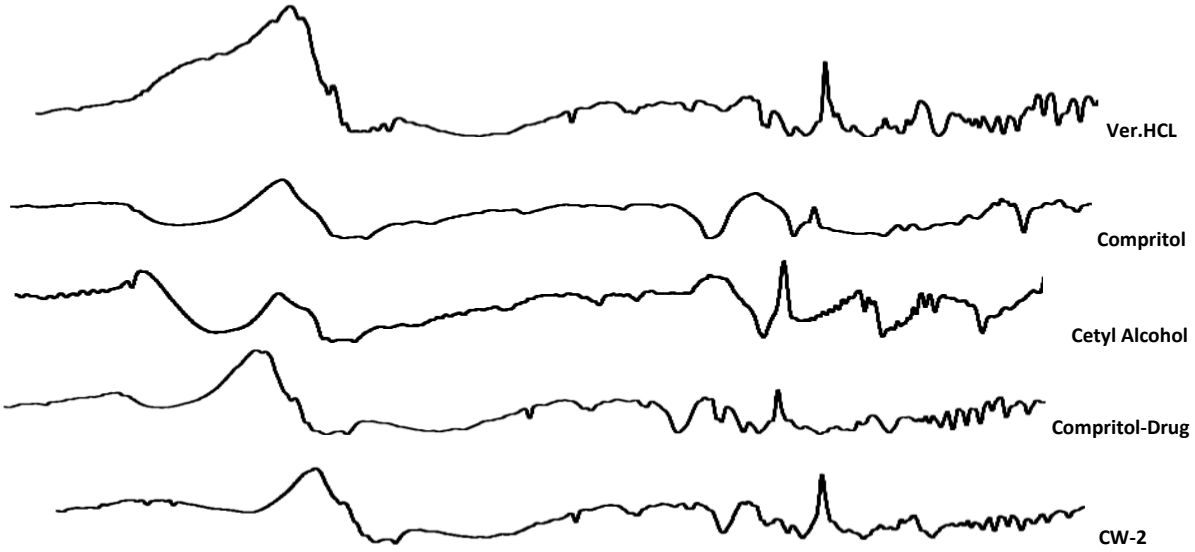

Fig No-1- IR spectra of Drug & Excipeints

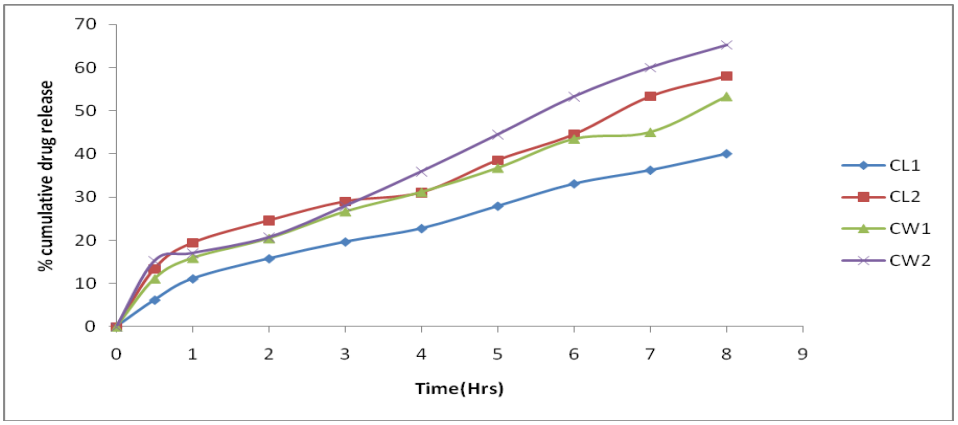

Fig No-2 Percentage cumulative drug release of formulation

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