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FORMULATION AND EVALUATION OF VALSARTAN SUSTAIN RELEASE TABLETS USING HYDROPHILIC POLYMERS

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ABSTRACT

The aim of this work is to design oral sustained release tablets of using hydrophilic polymers, and thus increasing patient compliance by reducing its frequency of administration. Tablets were prepared by wet granulation technique using hydroxypropyl methylcellulose, ethyl cellulose and carbopol. The compatibility of the drug with the various used excipients was studied using FTIR. The effects of polymer concentration, polymer viscosity and binary mixtures of some polymers on the in vitro drug release were studied. Results of FT-IR confirmed drug-excipients compatibility. The different prepared tablet formulae exhibited content uniformity within the acceptable limit and showed good mechanical properties. The stability studies showed that the drug content for the best formulation remained same even after storing for three month at different temperatures.

Key words: Valsartan, hydroxypropyl methylcellulose, ethyl cellulose, carbopol, sustain release

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INTRODUCTION

The mechanism of drug release from hydrophilic matrix tablets following ingestion is complex, but is known to be based on dissolution of the drug (if soluble), diffusion of the drug through the hydrated portion of the matrix and erosion of the Outer hydrated polymer on the surface of the matrix typically, when the matrix is exposed to an aqueous solution or Polymer (surface layer). The core of the tablet remains essentially dry at this stage. In the case of a highly Soluble, high – dose drug, this phenomenon may lead to an initial burst release because of the presence of the drug on the surface and periphery of the matrix tablet. The gel layer, (rubbery state) grows with time as more water permeates into the core of the matrix, increasing the thickness of the gel layer and providing a diffusion barrier to drug release. Simultaneously, as the outer layer becomes fully hydrated, the polymer chains become completely released and can no longer maintain the integrity of the gel layer, leading to disentanglement and erosion from the surface of the matrix. Water continues to penetrate towards the core of the tablet, through the gel layer, unit it has been completely eroded. Were as soluble drugs are released by this combination of diffusion and erosion

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mechanisms, erosion is the predominant mechanism for insoluble drugs, regardless of dose. For successful ER of drugs, either soluble or insoluble, it is essential that polymer hydration and surface gel layer formation are quick and consistent to prevent immediate tablet disintegration and premature drug release. For this reason, polymers for hydrophilic matrices can be supplied in small particle size ranges to setter ensure rapid hydration and consistent formation of the gel layer on the surface of the tablet.

Valsartan is an angiotensin II receptor antagonist that is used for the treatment of hypertension. It treat the hypertension by blocking the vasoconstrictor and aldosterone secreting effect of angiotensin II selectively by blocking the binding of angiotensin II and angiotensin I receptor in many tissues. The most preferred route for this drug is oral delivery in form of tablets. Valsartan have poor water solubility, low bioavaibility (approximately 20-25%), and shorter half-life (nearly 6 h) (1-4).

MATERIALS AND METHODS

MATERIALS : Valsartan (Val) was obtained as a gift sample from Torrent Pvt Ltd, Hydroxy propyl methyl cellulose, Ethyl cellulose, Carbopol, Lactose, Magnesium Stearate, Talc, Potassium dihydrogen phosphate, Acetic acid, Perchloric acid, Disodium hydrogen phosphate from SD Fine Chemicals, Mumbai Pvt Ltd, India.

METHODS -Preformulation studies

Preformulation testing is an investigation of physical and chemical properties of drug substances alone and when combined with pharmaceutical excipients. It is the first step in the rational development of dosage form (5).

Compatibility studies (Fourier Transform Infrared Spectroscopic studies)

One of the requirement for the selection of suitable excipients or carrier for pharmaceutical formulation is its compatibility. Therefore in the present work a study was carried out by using FT-IR spectrophotometer to find out if there is any possible chemical interaction of valsartan with Hydroxy propyl methyl cellulose, Ethyl cellulose, Carbopol (5).

Characterization of Granules -Angle of Repose

The angle of repose of granules, was determined by the fixed funnel and freestanding cone method, according to the method (6) where by accurately weighed granules (3gm were carefully poured through the funnel with its tip at 2 cm height (h) until the apex of the conical heap so formed just reached the tip of the funnel. The mean diameter (r1, of the base for the powder cone was measured and angle of repose (0) was calculated using the following equation.

$\theta = \tan^{-1} (h/r)$ Where, θ = angle of repose; h = height; r = radius

Bulk Density

Both loose bulk Density and tapped bulk density were determined, according to the method reported by Raghu ram et al, Whereby a quantity (3g) of granules from each formula, previously lightly shaken to break any agglomerates cylinder. After the initial volume was observed, the cylinder was allowed to full under its own weight onto a have surface from the height of 2.5cm at 2-Second intervals. The tapping was continued until no further change in the volume was noted LBD and TBD were calculated using the following formulas

LBD = Weight of the powder/ volume of the packing; TBD = weight of the powder / tapped volume of the packing

Preparation of matrix tablets

Valsartan tablets with different concentrations of polymer were prepared by the wet granulation technique (Table-1).

Ingredient	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**	**F13**	**F14**
Drug	20	20	20	20	20	20	20	20	20	20	20	20	20	20
Ethyl cellulose	15%	%10	%10	%5	----	----	%5	----	%10	----	%10	%5	%5	----
Carbopol	15%	10%	%10	%5		%15	%5	---	---	----	%10	%5	---	----
HPMC	----	----	----	%15	%10	%15	----	%10	%5	%5	----	%10	---	%10
Lactose	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%
Talc	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%
Mg.Ste	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%

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Characterization of Tablets

The properties of the compressed matrix tablet, such as Hardness, Friability, weight variation and drug content Uniformity (7).

Hardness Test

For each formulation, the hardness of 5 tablets was determined using a Monsanto hardness tester, mean and SD were calculated

Friability Test

For each formulation, 6 tablets were weighed. The tablets were placed in a friabilator (Roche friabilator) and subjected to 25 rpm in 4 minutes. The tablets were then declusted and reweighed. The friability was calculated as the percentages weight loss.

F = 100 (1-wo/wt) Where, Wo = weight of tablets before friability test, Wt = weight of tablets after friability test

Weight variation Test

To study weight variation, to tablets of each formulation were weighed using an electronic balance and the test was performed according to the USP official limits of percentage deviation of tablet are presented in the table-2.

Table-2 Weight variation Tolerance for uncoated Tablets

Average weight of Tablets (mg)	Maximum percentage Difference Allowed
130 or less	10
130 – 324	7.5
More than 324	5

In-Vitro Drug Release Studies (Dissolution studies)

The release of valsartan from the SR tablet was studied in 900 ml of phosphate buffer pH 6.8 as dissolution medium using a USP dissolution paddle assembly at 50 rpm and $37^o \pm 0.5^o$ C. An aliquot (1 ml) was withdrawn at specific time intervals, filtered and diluted to 10 ml with phosphate buffer pH 6.8, and drug content was determined by UV-visible spectrophotometer at 252 nm. An equal volume of fresh dissolution medium was replaced to maintain the dissolution volume.

Dissolution studies were performed 3 times for a period of 12 hrs and the mean value were taken. Cumulative percentage of drug release was calculated using an equation obtained from a standard curve.

RESULTS AND DISCUSSION

The IR spectra of all the tested samples showed the prominent characterizing peaks of pure drug valsartan HCl, individual polymers, hydroxypropyl methylcellulose, ethyl cellulose and carbopol and the admixture of drug and polymers and was confirmed that no chemical modification of the drug has been taken place and thus they were proved to be compatible with each other and hence suitable for preparation of sustained release tablets.

Standard Curve of valsartan was determined by plotting absorbance (nm) verses concentration (mcg/ml) at 252 nm and it is follows the Beer's law. The results are given in table-3, are as follows: -

Table-3 Data's for Calibration Curve of valsartan In phosphate buffer 6.8

S. No.	**Concentration** (mcg/ml)	**Absorbance** (237 nm)
1.	0	0
2.	5	0.184
3.	10	0.372
4.	15	0.603
5.	20	0.791
6.	25	0.971
Slope		**0.0413**
Regression		**0.9991**

The regression value is 0.9991, and slope is 0.0413.

Characterization of Granules

Angle of repose

Angle of repose ranged from 22^o 64"± 1.1968 to 28^o69"±1.847. The results were found to be below 30^0 and hence the blend was found to have good flow ability.

Bulk density and tapped density:

Bulk and tapped densities are used for the measurement of Compressibility index. The LBD and TBD ranged from 0.233± 0.006 to 0.313±0.016 and 0.257± 0.005 to 0.358±0.020 respectively

Hauser's Ratio

The Hauser ratio ranged from 1.12± 0.081to 1.200± 0.114. The result indicates the free flowing properties of the granules.

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Physical Evaluation of Sustained-Release Tablets of Valsartan

The hardness of all batches ranged from 7.38±0.46 - 7.99±0.58 Kg/cm$^{2.}$ The percentage friability of all batches ranged from 0.139 % to 0.189 %. Drug content was found to be uniform among the all formulations and ranged from 98.98±0.24 to 99.45±0.34

***In Vitro* Drug Release Studies**

The *in-vitro* drug release studies were conducted using pH 6.8 phosphate buffer solution as dissolution medium and the results were tabulated and also represented graphically by taking Time (hrs) on X-axis and Cumulative percentage drug release on Y-axis.

The *in- vitro* drug release studies showed better sustained and prolonged release with all the particles for about 12 hrs while F-12 formulation showed better release (Fig-1-4).

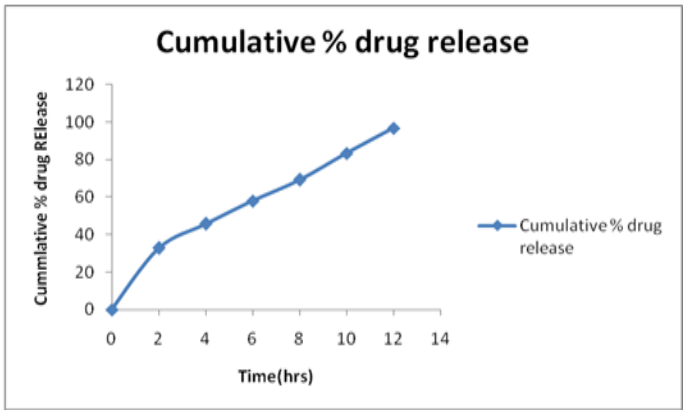

Fig-1 Cumulative % drug release (F-12)

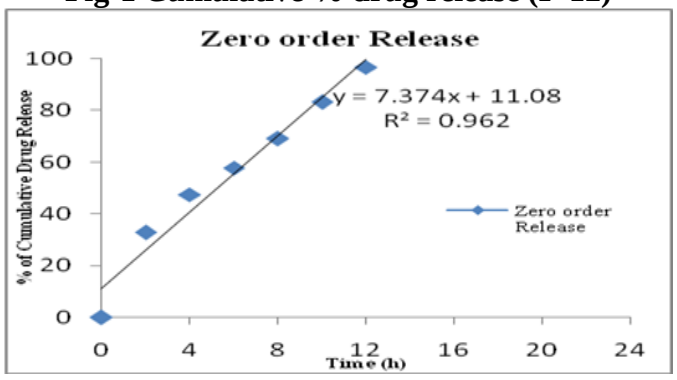

Fig-2 Zero order release (F-12)

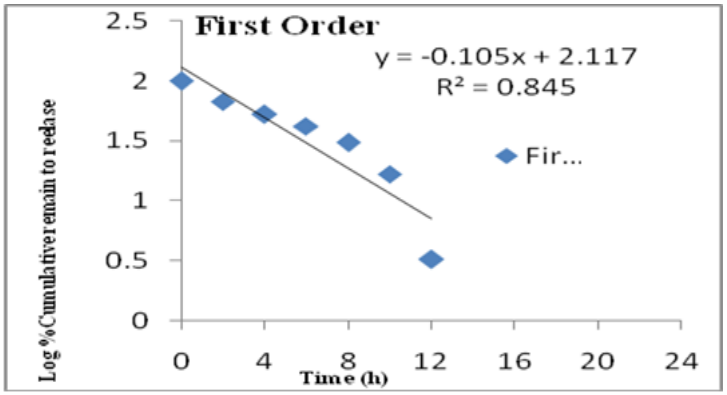

Fig-3 First order release (F-12)

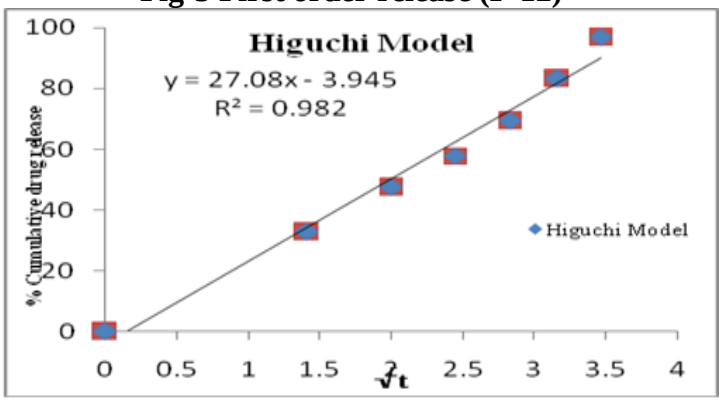

Fig-4 Higuchi model (F-12)

Conclusion

From results it was concluded that valsartan with hydrophilic polymers combination in equal proportions may be a promising form of drug delivery by which the total dose and frequency of drug administration may be considerably reduced thereby improving efficacy.

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