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Development and Evaluation of Fast Dissolving Tablets of Valsartan Using Different Binders

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ABSTRACT

The aim of present work was to develop fast dissolving tablets of Valsartan by direct compression method using different binders such as acacia, sucrose, starch, gelatin, hydroxypropyl methylcellulose (HPMC) H7509, and Polyvinyl-pyrrolidone (PVP). During the compression of tablets, binders keep the composition of these fast dissolving tablets together. The right selection of binder or combination of these is essential to maintain the integrity and stability of the tablet. The prepared tablets were evaluated for parameters such as hardness, friability, drug content, weight variation, wetting time, water absorption ratio, in-vitro disintegration time, *in vitro* dissolution studies and stability studies. The study reveals that formulations prepared by direct compression (F5) exhibits better dissolution (90.57%) with lowest disintegration time (40 seconds) containing sucrose as binding agent.

Keywords: Fast dissolving tablets, Superdisintegrants, Direct Compression, Disintegration

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INTRODUCTION

Despite great innovations in drug delivery, the oral route remains the preferred route for administration of therapeutic agents because of accurate dosage, low cost therapy, self-medication, noninvasive method, and ease of administration leading to high level of patient compliance[1]. The most popular dosage forms are conventional tablets and hard gelatin capsules. One important drawback of such dosage forms is dysphagia; almost 50% of the population is affected by such problem. Hence, patients do not comply with prescription, which results in high incidence of noncompliance and ineffective therapy[2]. Recently, fast disintegrating drug delivery systems have started gaining popularity and acceptance as new drug delivery systems, because they are easy to administer and lead to better patient compliance[3]. In some cases such as motion sickness, sudden episodes of allergic attacks or coughing, and unavailability of water, swallowing conventional tablets may be difficult. This difficulty is particularly experienced by pediatric and geriatric patients. To overcome such problems, fast disintegrating tablets (FDTs) or orally disintegrating tablets have emerged as an alternative dosage form[4]. Recent advances in novel drug delivery systems (NDDS) aim for enhancing the safety of a drug molecule while maintaining its therapeutic efficacy so as to achieve better patient compliance[5]. The bioavailability of drugs may be increased due to absorption of drug in oral cavity and also due to pregastric absorption of saliva containing dispersed drugs that pass down into the stomach. Moreover, the amount of drug that is subjected to first-pass metabolism is reduced as compared to standard tablet[6]. The target populations for these new fast-dissolving/disintegrating dosage forms have generally been pediatric, geriatric, and bedridden or mentally disabled patients. Patients with diarrhea, persistent nausea, or vomiting, who are traveling, or who have little or no access to water are also good candidates for FDTs[7,17]. Valsartan is an angiotensin-receptor blocker (ARB) that may be used to treat a variety of cardiac conditions including hypertension, diabetic nephropathy and heart failure. Valsartan lowers blood pressure by antagonizing the renin-angiotensin-aldosterone system (RAAS); it competes with angiotensin II for binding to the type-1 angiotensin II receptor (AT1) subtype and prevents the blood pressure increasing effects of angiotensin II. Unlike angiotensin-converting enzyme (ACE) inhibitors, ARBs do not have the adverse effect of dry cough. Valsartan may be used to treat hypertension, isolated systolic hypertension, left ventricular hypertrophy and diabetic nephropathy. It may also be used as an alternative agent for the treatment of heart failure, systolic dysfunction, myocardial infarction and coronary artery disease [9]. Thus, FDTs would serve as an ideal dosage form for pediatric

patients who find it difficult to swallow the tablets[8]. Hence, an effort was made for preparation of fast disintegrating tablet of valsartan with an aim of enhancing patient convenience and compliance, reducing the lag time and providing faster onset of action.

MATERIALS AND METHOS

Valsartan obtained as a gift sample from Macleods Pharmaceutical Ltd. Acacia, Sucrose, Starch, Gelatin, H.P.M.C, P.V.P K40, Sodium Starch Glycolate, Talc, Magnesium stearate were of pharmacopeial grade and used as supplied by Loba Chemie, India.

Formulation of Tablets

Tablets containing 40 mg of valsartan were compressed by wet granulation method. The required quantities of valsartan, lactose and the selected binder were taken in mortar and mixed by geometric dilution technique. Total weight of the tablet to be kept constant, i.e., 200mg[10].

Table 1: Formulation of Valsartan Tablets

Ingredients	F1	F2	F3	F4	F5	F6
Valsartan	40 mg	40 mg	40 mg	40 mg	40 mg	40 mg
Lactose	125 mg	125 mg	125 mg	125 mg	125 mg	125 mg
P.V.P	5 mg	--	--	--	--	--
H.P.M.C	--	5 mg	--	--	--	--
Gelatin	--	--	5mg	--	--	--
Starch	--	--	--	5mg	--	--
Sucrose	--	--	--	--	5 mg	--
Acacia	--	--	--	--	--	5 mg
SSG	16 mg	16 mg	16 mg	16 mg	16 mg	16 mg
Talc	7 mg	7 mg	7 mg	7 mg	7 mg	7 mg
Mg Stearate	7 mg	7 mg	7 mg	7 mg	7 mg	7 mg
Total	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg

Evaluation

Angle of repose

Angle of repose was calculated using funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. The radius of the heap (r) was measured and angle of repose was calculated as per the formula [11,18].

$$\Theta = \tan^{-1} \frac{h}{r}$$

Bulk Density

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weight powder (passed through standard sieve # 20) into a measuring cylinder and initial

weight was noted. This initial volume is called the bulk volume. From this the bulk density is calculated according to the formula mentioned below. It is expressed in g/ml and is given by

$$Db = M/Vb$$

Where, Db is the bulk density, M is the mass of powder and Vb is the bulk volume of the powder [12, 13].

Tapped Density

It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times and the tapped volume was noted if the difference between these two volumes is less than 2%. If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2 % (in a bulk density apparatus). It is expressed in g/ml and is given by

$$Dt = M/Vt$$

Where, Dt is the bulk density, M is the mass of powder and Vt is the tapped volume of the powder [12, 13].

Carr's Index (CI)

Tapped and bulk density measurements can be used to estimate the Carr's index of a material. Carr's index was determined by

$$I = \frac{Dt - Db}{Dt} x\ 100$$

Where, Dt is the tapped density of the powder and Db is the bulk density of the powder. [13]

Hausner's Ratio

It indicates the flow properties of the powder and is measured by the ratio of tapped density to the bulk density.

Hardness

Six tablets are taken from each formulation these tablets are kept between the two jaws of a Monsanto harness tester, and pressure is applied by screwing its base, which is connected to lower jaw.[14,19]

Friability

Friability of tablets was determined in a Roche friabilitor. 20 tablets, previously weighed are taken in the plastic chamber of the laboratory friability tester. 20tablets are subjected to abrasion and shock by rotating the plastic chamber at 25 rpm for 4 min or 100 revolutions. The tablets are

dusted and reweighed. Differences between the initial weight and final weight determines friability. [14,19]

Drug Content

20 tablets were taken and powdered accurately. Powder containing equivalent to 40mg of Valsartan was taken and shake it with 60ml methanol in 200ml volumetric flask and dilute to volume with methanol. 5ml of this solution was taken and diluted up to 100ml with methanol and was analyzed spectrophotometrically.[15]

Disintegration time

To test the disintegration time, one tablet is placed in each tube, and the basket rack assembly is positioned in a 1-litre beaker of water (used as dissolution media) at 37°C±0.5°C, such that the tablet remains 2.5 cm from the bottom of the beaker.[15]

Dissolution Studies

The dissolution rate study of valsartan tablets was studied by using dissolution apparatus, which contains 900ml of phosphate buffer pH 7.4 and paddles rotates at 50rpm. The temperature was maintained at 37± 0.5˚C throughout the experiment. 5ml of dissolution media was withdrawn through a filter (0.45µ) at regular time intervals. Samples were diluted and assayed for valsartan at 250nm. The withdrawn sample was filled with fresh fluid. Each dissolution rate replicated three times (n=3).

Stability Studies

The best formulation was charged for stability studies at temperature and relative humidity of 40°C/75%RH for a period of one month. The parameters used to assess the effect of stress conditions on tablets include: Friability, Hardness, Disintegration time, and drug content[16].

RESULTS AND DISCUSSION

Fast disintegrating tablets have better patient acceptance and offer improved biopharmaceutical properties, improved efficacy and better safety as compared with conventional oral dosage forms. By using new manufacturing technologies, many drugs can be formulated in the form of fast disintegrating tablets to provide the advantages of liquid medication in the form of solid preparation. FDT need to be formulated for pediatric, geriatric, bedridden, psychotic patients, for those patients who are busy in travelling, patients who are may not have access to water. The development of a fast-dissolving tablet also provides an opportunity for a line extension in the market place; a wide range of drugs (e.g., neuroleptics, cardiovascular drugs, analgesics, antihistamines, and drugs for erectile dysfunction) can be considered candidates for this dosage

form. The composition of different formulations are presented in Table 1. Evaluation parameters like Angle of Repose, Tapped Density, Bulk Density, Hausner's Ratio, Carr's Index, were found to be satisfactory and the results are presented in Tables 2, while drug content, friability, hardness and disintegration time for the prepared batches of tablets are presented in table 3. The disintegration time of various batches showed wide variation, indicating that the type of super disintegrant had an effect on disintegration time. The formulation F5 containing Sucrose (as a binding agent) and SSG (as superdisintegrant) showed significantly decrease in disintegration time (40 seconds) among all the formulation. The porous structure induced in the tablet matrix was responsible for faster water uptake, thus allowing faster disintegration which has also been reported in the literature. When Acacia, PVP, SSG, CCS were used alone in the formulations, disintegration time noticed more than 1 minute. *In Vitro* dissolution rate study showed that at 5 minutes of study, F1-F6 formulation showed release rate in the range of 5-35% but at 10 minutes of dissolution study, release rate increased to 58.37% for F5 formulation (Figure 2).Release rate for F5 formulation was around 98% at the end of 60min which was less than 70% in rest of the batches indicating that F5 can be said as best combination for binder and superdisintegrant for FDTs of Valsartan. Stability studies were carried out with most satisfactory formulation F5 at 45°C/75%RH for one month. Samples were evaluated at various intervals of time (0, 7, 14, 21 and 30 days) and the results are presented in Table 4, which showed that there was no significant change in the parameters. Hence, formulation F5, was considered to be highly stable.

Table 2: Results for powder of various batches of formulations

Formulation	Angle of Repose	Tapped Density (gm/ml)	Bulk Density (gm/ml)	Hausner's Ratio	Carr's Index (%)
F1	33.79	0.594	0.465	1.25	20.52
F2	32.24	0.406	0.427	1.15	15.12
F3	30.65	0.417	0.314	1.19	18.91
F4	31.14	0.543	0.385	1.28	22.83
F5	29.31	0.572	0.398	1.33	25.20
F6	28.35	0.528	0.359	1.46	29.65

Table 3: Results of tablets prepared in various batches of formulations

Formulation	Drug Content (mg/tab)*	Hardness (kg/sq.cm)*	Friability (%) *	Disintegration Time (seconds) **
F1	38.0±0.3	4.0±0.73	0.5±0.24	130±1.85
F2	39.3±0.2	3.5±0.29	0.4±0.05	170±2.76
F3	38.3±0.4	4.5±0.35	0.6±0.29	290±1.99
F4	39.7±0.1	4.0±0.61	0.7±0.06	350±1.86
F5	39.3±0.2	3.0±0.21	0.6±0.02	40±1.38
F6	38.4±0.5	3.5±0.29	0.9±0.27	120±1.45

Values are expressed as mean±SD, *n=3, **n= 6

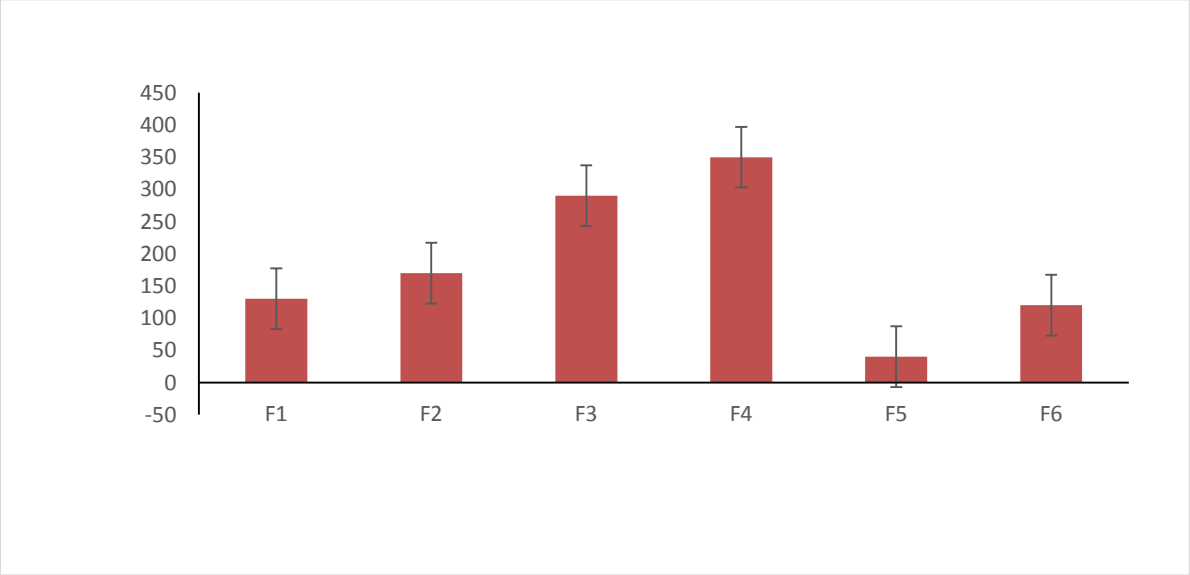

Figure 1: Disintegration time of various batches containing different superdisintegrant and its combination.

Table 4: Stability studies of fast dissolving tablets of Valsartan of Batch F5.

Value expressed in mean±SD, n=3

S.No	Parameter	At 0 Day	At 7th day	At 14th day	At 21st day	At 30th day
1	Hardness (kg/sq.cm)	3.0±0.61	3.0±0.58	3.0±0.62	3.0±0.54	3.0±0.56
2	Friability (%)	0.64±0.04	0.66±0.02	0.70±0.01	0.68±0.03	0.71±0.02
3	Disintegration Time (min)	0.40±1.07	0.88±0.75	1.15±1.10	2.40±0.40	2.60±1.17
4	Drug Content (mg/tab)	39.3±0.4	39.2±0.1	39.2±0.2	39.2±0.4	39.2±0.5

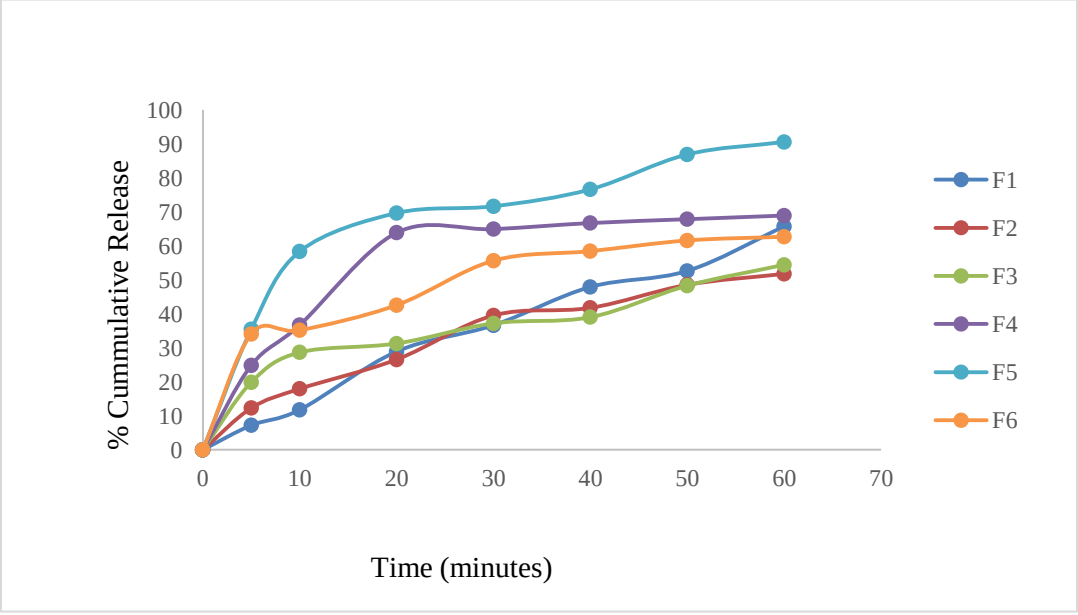

Figure 2: Comparative study of % Cumulative Release of Various Batches of FDT

CONCLUSION

More and more research is being conducted in the field of FDT and various advanced technology is being used in manufacturing of FDTs. An optimized Fast Disintegrating tablet was being prepared in this study by direct compression method using suitable combination of Sucrose and Sodium Starch Glycolate (SSG). The proposed FDT formulation possess ideal and reproducible characters of disintegration time and enhanced dissolution, which can lead to a better patient compliance.

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