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Original Article

Design of Fast Dissolving Urapidil Tablet Formulations

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ABSTRACT

The demand for fast disintegrating tablets has been growing, during the last decade especially for geriatric and paediatric patients because of swallowing difficulties. Urapidil is a new generation of sympatholytic antihypertensive (class-II) available in European market. Hence in present work an attempt has been made to formulate fast dissolving tablets of urapidil by direct compression technique using various concentration of Superdisintegrants like Cross carmellose sodium (Ac-Di-Sol), Polyplasdone R-XL and Sodium starch glycolate (SSG). The formulated tablets were evaluated for Crushing strength, Friability, Thickness, Diameter, Weight variation, Drug content, Wetting time, Water absorption ratio, Disintegration time and Percentage of drug release. All formulations showed satisfactory result. Among them formulation AD3 containing 3% of Ac-Di-Sol exhibited complete release within 1 hour and disintegration time within 10 second. Accelerated stability study indicated no significant difference in assay and crushing strength. There was no chemical interaction between the drug and excipients during FT-IR study and DSC study considered in the present investigation.

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1. INTRODUCTION

Oral drug delivery is the most widely utilized routes for administration that have been explored for systemic delivery of drug via various pharmaceutical products of different dosage form. Among them the most popular solid dosage forms are tablets and capsules which are simple and convenient to use. One of the important drawbacks of these dosage forms is difficult to swallow for geriatric, paediatric or psychiatric patients. Thus, a great attention has been paid for designing of mouth dissolving drug delivery systems (MDDDS) with fast disintegrating and or dissolving properties to improve patient's compliance.[1]A fast dissolving tablet (FDT) system can be defined as a dosage form for oral administration, which when placed in mouth, rapidly dispersed or dissolved and can be swallowed in the form of liquid. [2,3] Recently fast dissolving formulation is popular as novel drug delivery systems because they are easy to administer to the elderly patients and children having difficulty to swallow and also evident in travelling patients who may not have ready access to water. [4]As the tablet disintegrates in mouth, this could enhance the clinical effect of the drug through pre-gastric absorption through mouth, pharynx and oesophagus, as well as, bioavailability of drug can significantly be increased by avoiding first pass liver metabolism.

Urapidil, chemically described as 6-({3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl}amino)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione, is an α_1-adrenoceptor antagonist and as an 5-HT_{1A} receptor agonist. Oral bioavailability is 78% (range 72 to 84%) and distribution half-life and terminal half-life are about 35 minutes and 3 hours, respectively. [5, 6] Numerous studies have been carried out for the designing and fabrication of fast dissolving tablets (FDT) formulations using super disintegrants. Thus, an attempt has been made to formulate the FDT of Urapidil by Ac-di-sol, Polyplasdone R-XL and Sodium starch glycolate (SSG).

2. MATERIALS AND METHODS

*2.*1 Materials

Urapidil was procured as gift sample from cipla Ltd, Mumbai, India. Cross carmellose sodium (Ac-Di-Sol) and sodium starch glycolate (SSG) were purchased from Signet chemical corporation Mumbai, India. Polyplasdone R-XL was purchased from Orchid Healthcare, Chennai, India. Microcrystalline cellulose (Avicel-102), Mannitol and Sodium saccharine and Sodium lauryl sulphate (SLS) were procured from SD Fine chemicals, Mumbai, India. Colloidal silicon dioxide (Aerosil-R 972) and talc were purchased from Tangmin industry Ltd, China. All chemicals and solvents used are of high analytical grade.

2.2 Method of preparation of FDT

Urapidil, Ac-di-sol, Polyplasdone R-XL, SSG, SLS, Mannitol and Avicel-102 were passed through #40 mesh and collected separately in polyethylene bag. [7] Direct compression technique was adopted for batch preparation of FDTs. The drug and diluents were mixed in a geometrical manner and blended for a period of 20 minutes. The resulted mixture lubricated with Aerosil-R 972 and with talc (sifted through #60 mesh) for 5 minutes in Octagonal Blender (Mevish engineering, India). Finally the blend was compressed to formulate tablets using tablet compression machine (Cadmach Machinery Pvt. Ltd, India) with 6.5 mm circular flat punch. The composition of various formulations designed in the present study are given in Table 1.

2.3 Micromeritic properties of blended powder

Prior to compression, granules were evaluated for their micromeritic parameters. [8]Angle of repose was determined by funnel method. Bulk density (BD) and tapped density (TD) were determined by cylinder

Table 1: Composition of tablet formulations (mg)

		FORMULATIONS								
Sl no	**Ingredients (mg)**	**AD1**	**AD2**	**AD3**	**PL1**	**PL2**	**PL3**	**SSG1**	**SSG2**	**SSG3**
1	Urapidil	10	10	10	10	10	10	10	10	10
2	AC-di-sol	2	4	6	-	-	-	-	-	-
3	Polyplasdone R-XL	-	-	-	2	4	6	-	-	-
4	SSG	-	-	-	-	-	-	2	4	6
5	Avicel-102	100	98	96	100	98	96	100	98	96
6	Mannitol	40	40	40	40	40	40	40	40	40
7	SLS	1	1	1	1	1	1	1	1	1
8	Sodium saccharine	1	1	1	1	1	1	1	1	1
9	Aerosil R 972	1	1	1	1	1	1	1	1	1
10	Talc	2	2	2	2	2	2	2	2	2
	Total weight (mg)	**157**	**157**	**157**	**157**	**157**	**157**	**157**	**157**	**157**

method, and Carr's index (CI) was calculated using the following equation

CI= (TD-BD)/TD ×100..... (1)

Hausner's ratio (HR) was calculated by the following equation

HR=TD/BD..... (2)

2.4 Physiochemical characterization of Tablets

The physical properties such as *crushing strength, friability, thickness, diameter, weight variation, drug content, wetting time, water absorption ratio* and *disintegration time* for each formulation were determined.

Tablet crushing strength was determined by randomly selected 10 tablets using a digital crushing strength tester (Erweka TBH-28) and the data reported is the mean of three individual determinations. [9]

Friability.

Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Preweighed randomly selected twenty tablets were placed in a Roche friability tester and operated for 4 min at 25 rpm. Compressed tablets should not lose more than 1% of their weigh. [10]

Thickness and diameter.

Tablet thickness and diameter were measured by Vernier callipers (Mitatoyo, Japan). [11]

Weight variation.

A weight variation test was performed according to USP30 NF25 on 20 tablets by taking samples from a batch after production of every 100 tablets and randomly from a total batch of 300 tablets using an electronic balance (Contech Instruments CA 224, India). [12]

Drug content.

The drug content in terms of assay of each batch was determined in triplicate. For each batch a number of 20 tablets were weighed and crushed to fine powder using mortar and pestle. An accurately weighed of 10 mg of the powder was taken and suitably dissolved in methanol and analyzed by HPLC after making appropriate dilutions. The procedure was carried out on Shimadzu LC-10AT (Octadecylsilyl silicagel; 250 × 4.00 mm) with flow rate of 1.5 ml/minute at ambient temperature.

Wetting time and Water absorption ratio.

Twice folded tissue paper was placed in a Petri dish having an internal diameter of 6.5 cm to that 10 ml of purified water containing an eosin dye solution (0.05% w/v) was added to petrisish. A tablet was carefully placed on the surface of the tissue paper in the Petri dish. The time required for dye to reach the upper surface of the tablet and to completely wet was noted as the wetting time. Water absorption ratio (R) was then determined according to the following equation

$R= (W_a-W_b)/W_b \times 100$..... (3)

Where W_a and W_b are tablet weight after and before water absorption respectively. [12]

Disintegration time.

Many reports suggest that conventional DT apparatus may not give correct values of DT for FDTs. FDT is required to disintegrate in small amounts of saliva within a minute without chewing the tablet. In a simplest method to overcome these problems, 6 mL of phosphate buffer of pH 6.8 was taken in a 25-mL measuring cylinder. Temperature was maintained at 37±2°C. A FDT was put into it and time required for complete disintegration of the tablet was noted. [13]

In-vitro dissolution study

The procedure was determined using United States Pharmacopoeia (USP) XXIV dissolution testing apparatus II (paddle method). [14,15] The dissolution test was performed using 900 ml of 0.1N HCl (pH-1.2) at 37 ± 0.5°C and 50 rpm. A sample of 10 ml of the solution was withdrawn from the dissolution apparatus at 10 minute interval with the replacement of fresh dissolution medium for 20 minute. The samples were passed through a 0.45 μm membrane filter and diluted to a suitable concentration with phosphate buffer. The absorbance of these solutions was measured at 237 nm using a Shimadzu UV-1601 UV/Vis double beam spectrophotometer.

3. RESULTS AND DISCUSSION

3.1 Micromeritic properties of blended powder

Result shows that all the formulations produced optimal flow properties calculated in terms of compressibility. Table 2 depicts micromeritic properties of the designed formulations. The angle of repose ranged from 28.72±0.11 to 31.52 ± 0.09 which indicates optimal flow ability. In addition to that the tapped density and bulk density for all formulation granules ranged between 0.68±0.02 to 0.73±0.24 and 0.56±0.02 to 0.63±0.18 respectively, whereas Hausner's ratio was obtained between 1.2 to 1.27.

Insert Table 2 here

3.2 Physiochemical characterization of Tablets

The physical properties of the designed tablets are presented in Table 3. These properties were studied by determining crushing strength, friability, thickness, diameter, weight variation, drug content, wetting time, water absorption ratio and disintegration time. Crushing strength of prepared tablets ranged from 44.3±0.73 newton to 50.98±0.92 newton. The results were compared and concluded on the basis of amount of superdisintegrants and Avicel-102 used. It was observed that those formulations contained sodium starch glycolate exhibited higher hardness than others.[16] Morever the amount of Avicel-102 at 61% in all formulations showed higher crushing strength. The European and United States Pharmacopeia state that a loss up to 1% is acceptable for friability. Prepared tablets passed the friability test as values were ranged from 0.09% to 0.45% indicating the ability of tablet to withstand abrasion in handling packaging and shipment. The thickness for all tablets ranged between 2.80±0.20 to 2.83±0.19 mm and diameter was similar for all tablets. In a weight variation test, the pharmacopoeial limit for the percentage deviation for tablets of more than 150 mg is ±3.5 %. The average percentage deviation of all tablet formulations was found to be within the above limit and hence all formulations passed the test for uniformity of weight as per official requirements. Average weight of each formulation tablets ranged from 157 mg to 158 mg. Uniformity in drug content was found among different formulations of the tablets, and the percentage of drug content was more than 99% in all cases. During this study various disintegrants were used at 1%, 2% and 3% level. The results shown that concentration dependent disintegration time was observed in batches prepared using superdisintegrants. Among them Ac-Di-Sol based formulations (AD3 at 3% level) exhibited

lesser disintegration time (10±1.10sec.). Because the fibrous nature of Ac-Di-Sol gives it out-standing water wicking capabilities and it crosslinked chemical structure creates an insoluble hydrophilic, highly absorbant material with good swelling properties.; hence it facilitates faster disintegration.[17] Water absorption ratio and wetting time, which are important criteria for understanding the capacity of disintegrants to swell in presence of little amount of water were found to be in the range of 72.46±0.39 to 88.71±0.29 % and 14±1.2 to 41±0.48 second respectively.[18]

Table 2: Micromeritic properties of prepared powder blend

Formulations	Bulk density	Tapped density	Angle of repose	Hausner´s ratio	Carr´s index
AD1	0.60±0.01	0.68±0.02	28.72±0.11	1.27	13.7
AD2	0.62±0.12	0.70±0.01	30.23±0.03	1.19	15.71
AD3	0.61±0.04	0.72±0.01	30.45±0.26	1.26	17.66
PL1	0.57±0.11	0.70±0.23	29.31±0.05	1.2	16.71
PL2	0.63±0.04	0.71±0.03	32.26±0.27	1.18	15.08
PL3	0.58±0.04	0.69±0.12	29.46±0.46	1.21	18.39
SSG1	0.56±0.02	0.68±0.04	29.38±0.07	1.16	14.23
SSG2	0.62±0.06	0.73±0.02	30.45±0.34	1.22	18.88
SSG3	0.63±0.18	0.73±0.24	31.52±0.09	1.2	18.43

Data are represented as mean ± standard deviation (SD),n=3

3.3 In-vitro dissolution study

Different grades of superdisintegrants ranging 1, 2 and 3 percentages were used to formulate FDT of urapidil tablets and those formulations were subjected to *in-vitro* drug dissolution studies. All formulation released 38% of drug within 10 minute. Formulations based on Ac-di-sol at 3% level showed complete release within 1 hours whereas polyplasdone and SSG based formulations released complete drug within 2.5 and 3 hours respectively. Result showed that Ac-di-sol based formulations exhibited quicker drug release among all disintegrants. This could be due to higher water uptake and formation of channel in the tablet.[19] Hence on the basis of above result, AD3 was selected as promising formulation for further studies.

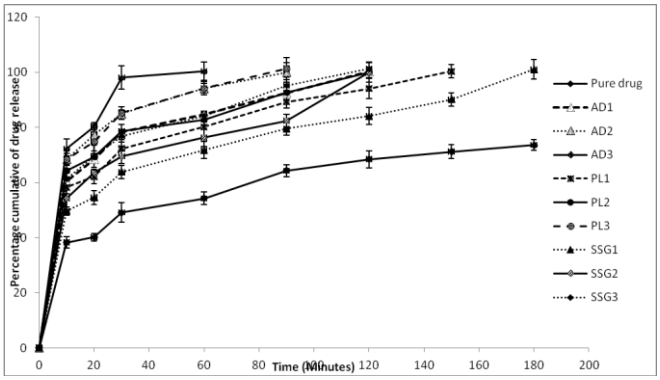

Fig 1: In-Vitro release profile of formulations

3.4 Drug polymer interaction study

The drug - excipient interaction were studied using FTIR (FTIR 8400S, Schimazu). [20, 21]IR spectra for drug and powdered tablets were recorded in a Fourier transform infrared spectrophotometer with KBr pellets. The spectra were scanned over 3600-400 cm-1 range. It was found that there was no chemical interaction between pure drug and excipients used as cited in figures 2 and 3.

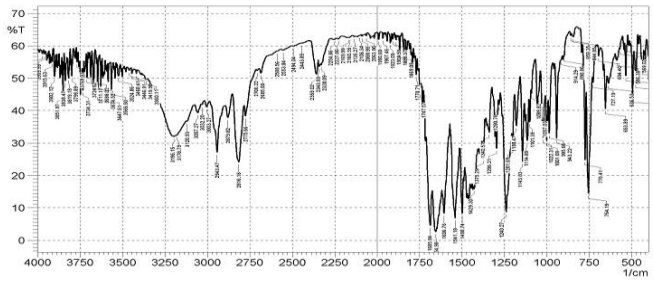

Fig 2: FTIR Spectrum of Pure drug

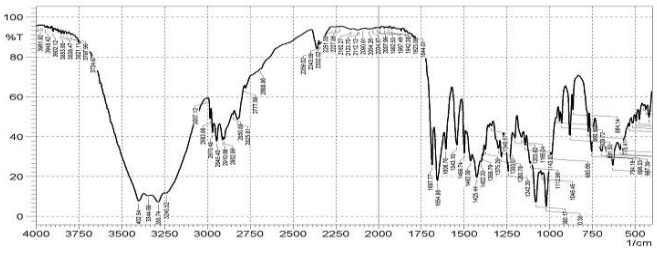

Fig 3: FTIR Spectrum of best formulation

3.5 Differential scanning colorimetry (DSC) study

The DSC analysis of pure drug and best formulation were carried out using Shimadzu DSC 60. The analysis was performed at a rate 10 ^{0}C min ranging from 20^{0}C to 400^{0}C temperature. Figures 4 and 5 showed, there

Table 3: Physical characterization of the designed formulations

	AD1	AD2	AD3	PL1	PL2	PL3	SSG1	SSG2	SSG3
Crushing strength (Newton)	44.3±0.73	47.8±0.54	48.5±0.71	46.3±0.85	48.7±0.46	47.6±0.56	46.9±0.61	51.7±0.83	50.98±0.92
Friability (% w/w)	0.4±0.004	0.3±0.002	0.45±0.001	0.1±0.021	0.09±0.008	0.19±0.08	0.23±0.008	0.17±0.07	0.13±0.06
Thickness (mm)	2.82±0.20	2.82±0.29	2.80±1.23	2.81±0.20	2.82±0.14	2.81±0.47	2.82±0.43	2.80±0.2	2.83±0.19
Diameter (mm)	6.51±0.26	6.50±0.44	6.51±0.26	6.50±0.22	6.50±0.12	6.51±0.32	6.50±0.09	6.50±0.22	6.50±0.18
Weight variation (mg)	157.2±0.31	157.2±0.52	157.3±0.27	158.7±0.73	158.26±1.23	157.6±1.36	157.1±1.42	158.3±2.41	157.2±0.56
Drug content (%)	99.98±1.23	100.03±0.98	101.38±0.56	100.93±0.99	100.07±1.13	99.97±1.03	99.93±0.83	100.73±0.92	100.68±0.42
Wetting time(Sec.)	28±0.34	20±0.12	14±1.02	31±0.43	26±0.72	20±0.28	41±0.48	31±0.43	27.67±1.01
Water absorption ratio(%)	82.21±0.35	86.27±0.73	97.12±0.28	79.64±1.01	84.11±0.82	88.71±0.29	72.46±0.39	77.49±0.52	80.46±0.64
Disintegration Time(Sec.)	25±0.46	19±0.83	10±1.10	28±1.03	22±0.73	13±0.94	33±0.72	25±1.02	20±1.02
% Drug release(10 Mnt.)	80.12±0.92	92.27±0.62	100.73±1.02	74.88±0.78	79.18±1.37	82.52±0.28	68.59±0.92	73.28±0.47	83.36±0.67

Data are represented as mean ± standard deviation (SD),n=3

was no change in endothermal peak observed with an additional peak, may be the presence of impurity.

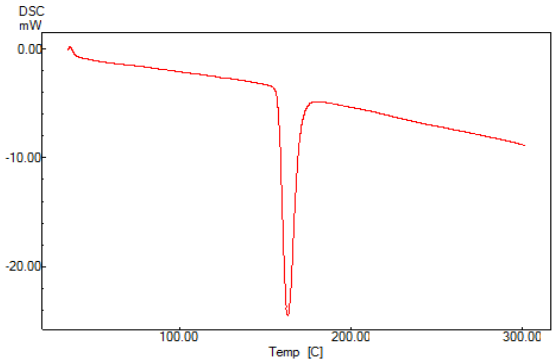

Fig 4: DSC Endothermal Peak of pure drug

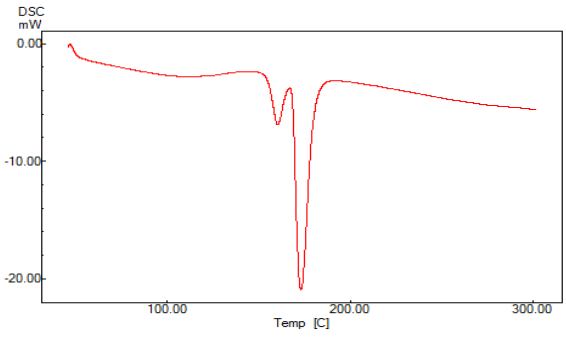

Fig 5: DSC Endothermal peak of best formulation

3.6 Stability study of best batch

Long term, intermediate and accelerated stability testing were carried out based on the ICH guidelines considering 25±2°C/60±5% RH, 30±2°C/65±5% RH and 40±2°C/75±5% RH respectively. One hundred tablets of batch AD3 were securely packed in aluminium blister and placed in humidity chamber. The samples were evaluated for crushing strength and drug assay at a regular interval of 3 months during the study of 24 month. There was no significance change in crushing strength and drug assay as shown in Table 4. Thus, F3 formulation batch confirmed its stability.[22, 23]

4. CONCLUSION

The present investigation shows that the various superdisintegrants can effectively be used to design fast dissolving tablet of Amlodipine besylate utilizing direct compression technique. The use of superdisintegrants for preparation of FDT is highly effective and commercially feasible. These superdisintegrants accelerate disintegration or

Table 4: stability study of best batch

Long term stability study (25± 2°C & 60±5% RH)				
Days (Month)	**3**	**6**	**9**	**12**
Drug assay (%)	101.39± 0.21	101.19± 0.43	101.46± 2.62	100.32± 1.07
Crushing strength (newton)	48.35±1 .25	48.06±1 .08	48.45±1 .37	48.33±2 .53

Intermediate stability (30± 2°C & 65±5% RH)				
Days (Month)	**3**	**6**	**9**	**12**
Drug assay (%)	101.47± 0.35	100.01± 1.12	100.38± 2.06	100.37± 2.72
Crushing strength (newton)	48.39±1 .45	48.88±2 .42	48.37±1 .93	48.19±2 .17
Accelerated stability (40± 2°C & 75±5% RH)				
Days (Month)	**1**	**2**	**3**	**6**
Drug assay (%)	100.35± 0.47	100.78± 2.42	99.52±3 .05	100.23± 3.45
Crushing strength (newton)	48.53±1 .07	48.68±1 .73	48.69±2 .08	47.11±2 .13

Data are represented as mean ± standard deviation (SD),n=3

dissolution of tablets by virtue of their ability to absorb a large amount of water when exposed to an aqueous environment. The physiochemical characterizations of all formulations were found to be satisfactory. Result shows formulation AD3 based on Ac-Di-Sol exhibited complete release within 1 hour. From dissolution study AD3 was selected as best laboratory scale grade batch. Hence reproducible production scale batches of size 1000 tablets were designed and charged for stability study. Parameters were checked and found to be within the specified limit. Furthermore the *in-vivo* and pharmacokinetic study have to carry out.

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