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Development and Characterization of Trandolapril Immediate Release Tablets Using Different Superdisintegrating Agents

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ABSTRACT

A potent non-sulfhydryl prodrug, trandolapril is transformed into the active substance, trandolaprilat, in the liver. For obese individuals with mild-to-moderate essential hypertension, Trandolapril is effective and safe. The elimination $t_{1/2}$ of trandolapril and trandolaprilat are approximately 6 hours and 16–24 hours, respectively. The goal of present work is to develop the Trandolapril immediate release tablet using various superdisintegrants. Crospovidone, Sodium starch glycolate and Croscarmellose sodium in concentrations of 2%, 4%, and 6% were used as superdisintegrating agents for the optimization. Direct compression technique was used to make nine formulations (IRTR 1 to IRTR 9). The powder blends of all batches were evaluated for different parameters to know the powder flow characteristics and it was found that the powder blend had excellent flow and compressibility characteristics. Then, compressed tablets were tested for quality control parameters as per the IP. In formulation IRTR1-IRTR9, disintegration time was observed 30.23 to 71.67 Sec and more than 70% drug was released in 30 min. Thus, based on evaluation results, it is concluded that formulation of immediate release (IR) tablets of Trandolapril were successfully developed. Minimum disintegration time 30.23 seconds 90.56% drug release in 30 min was obtained with IRTR3.

Key words: Trandolapril, Immediate release, Crospovidone, Sodium starch glycolate and crocarmellose sodium

1. INTRODUCTION

Trandolapril (non-sulfhydryl prodrug) (Figure.1) is a potent ACE inhibitor quickly get converted in the liver to the trandolaprilat.[1,2] It belongs to BCS II and BDDCS II.[3] Clinically, it is used to manage patients with CHF and myocardial infarction.[1,2] For overweight individuals with primary hypertension, trandolapril is also effective as well as safe.[2] Due to its strong affinity for ACE and high lipophilicity index, it is very effective when compared to other ACE (Angiotensin converting enzyme) inhibitors.[4] Trandolapril has an approximately 6-hour half-life.[1,5] The effective half-life of trandolaprilat is 16 to 24 hours at steady state.[1,5] Hence, Trandolapril is a good molecule for immediate release dosage form. 85% of the quantity that is labelled must dissolve within 30 minutes for a dosage form to be considered immediate release.[6] The use of superdisintegrants like Crospovidone, Sodium starch glycolate, and Croscarmellose sodium among other substances, is the fundamental method used in the composition of the tablet. After administration in the gut, these superdisintegrants offer instantaneous tablet breakdown. Consequently, reducing the breakdown time improves the rate at which drugs dissolve.[7] The delivery of drugs with an immediate effect is preferred for those with extended biological half-lives. This research work focused on the selection of suitable superdisintegrating agent with for development of oral immediate release tablets of Trandolapril, in order to reduce the onset of action for management of high blood pressure.

2. MATERIALS

Mylan Laboratories Limited, Hyderabad provided the gift sample of Trandolapril. All other chemicals used were analytical grade.

3. METHODS

Trandolapril immediate release tablets were produced as per the composition (Table 1). Different superdisintegrating agents, such as Crospovidone, Sodium starch glycolate, Croscarmellose sodium were used with a fixed amount of microcrystalline cellulose and manufactured using the direct compression technique.[8-11] MCC and directly compressible lactose as filler were passed through sieve number 40. Drug was combined using the geometric dilution technique with pre-sieved excipient mixture and various disintegrants. The pre-compressed powder mixture was tested for their flow behavior, including density of the blend (bulk and tapped), Hausner's ratio, compressibility index and angle of repose. Before the tablet compression, glidant and lubricant were added in blend and blended for 10 min. Tablets were compressed using the Rimek Mini Press-II MT Rotary Tablet 12 station Machine (Karnavati Engineering Ltd.).

3.1 Pre-Compression Evaluation of Powder Blend

3.1.1 Drug–Excipient Interaction Study by FTIR

The pure drug, drug-excipient mixture (1:1) were studied by spectroscopy method 12-13] using a FTIR [spectrophotometer (Bruker Alpha Model _Absorbance Mode).[17] KBr discs method was used and spectrums were analyzed in the range of 4000–400 cm–1 wave number.

3.1.2 Drug–Excipient Interaction Study by XRPD [12,13]

The XRPD studies were conducted using an X-ray powder diffractometer (D8 Advance XRD). X-ray powder diffraction patterns were recorded with scanning rate of 10°/min over a 2θ angular range of 5–80° with an increment of 0.05° was kept for obtaining.

3.1.3 Bulk Density [14,15]

A weighed amount of powder was poured into the graduated cylinder and the resulting volume was measured and bulk density was determined using the (Eq. 1). Tapped density was determined using bulk density test apparatus by setting the number of tapping 25, 50 and 75 until no further change in volume was noted and volume after tapping was measured (Eq. 2).

$$\rho_b = M/V_b \quad \text{…. Eq.1}$$

Where, ρ_b = Bulk density M = Mass of the powder, V_b = Bulk volume of the powder

$$\rho_t = M/V_t \quad \text{…. Eq.2}$$

Where, ρ_t = Tapped density M = Mass of the powder, V_t = Bulk volume of the powder

3.1.4 Hausner's ratio and Carr's index [14,15]

The Hausner's ratio (H_r) Eq. [3] is used to understand the flow behavior of powder or granular material in terms of ratio of tapped density and bulk density.[9]

$$H_r = \rho_t / \rho_b \quad \text{…. Eq.3}$$

Where, BD is the Bulk density of the powder, and TD is the Tapped bulk density of the powder.

Carr's Index (CI) is an indication of the compressibility and flow property of a powder. It is calculated by Eq. [4].

$$CI = \{(\rho_t - \rho_b)/ \rho_t\} \times 100 \quad \text{…. Eq.4}$$

3.1.5 Angle of repose (θ) [14,15]

The angle of repose value is also an indicator of powder flow characteristic. It is most commonly used by fixed height method. It is the angle between the powder pile's surface and the horizontal plane. The angle of repose was calculated using Eq. [5].

$$\text{Angle of repose } (\theta) = \tan^{-1} (h/r) \quad \text{….Eq. 5}$$

3.2 Post Compression Characterization of Tablets

3.2.1 Thickness [10]

Ten tablets from each batch were randomly taken and tablet thickness was determined using Vernier-caliper.

3.2.2 Weight variation [16]

Twenty tablets were randomly selected, weighed accurately using electronic balance and checked for the %Weight variation limit as reported in IP.[10] The average weights and standard deviations were calculated and reported as mean values ± SD.

3.2.3 Hardness [10]

The Monsanto hardness tester was used for accessing tablet hardness. Six tablets from each formulation were tested for hardness, and an average value was calculated in reported in kg/cm^2.

3.2.4 Drug content [17]

Tablets were powdered and equivalent to 10mg of drug, tablet powder were accurately weighed. Then drug was extracted and filtered and after required dilution, solution was estimated UV spectrophotometrically at λ max 223nm.

3.2.5 Disintegration test [16]

Disintegration test was carried out using tablet disintegration test apparatus (Electrolab, India) using distilled water as media at temperature 37±2°C.

3.2.6 In vitro drug release [17]

In vitro drug release study was performed using USP type II Dissolution apparatus (Electrolab, Mumbai, India). 900 ml 0.1 N HCl (pH 1.2) was taken as dissolution medium used at 37±0.5°C with 50 rpm paddle rotation. Pre-weighed Trandolapril tablets were introduced into the dissolution basket. Aliquots 5 ml were withdrawn at time interval of 5, 10, 20 and 30 min and same volume of fresh dissolution media were added in basket. The samples were passed through filter paper and samples absorbance was measured at 223 nm using UV-visible spectrophotometer against blank (0.1N HCl).

4. RESULTS AND DISCUSSION

Trandolapril immediate release tablets were successfully prepared by direct compression method as per formulation (Table 1) using different superdisintegrants i.e. Crospovidone (IRTR1 to IRTR3), Sodium starch glycolate (IRTR4 to IRTR6) and Croscarmellose sodium (IRTRI7 to IRTR9).

4.1 Drug- Excipient Compatibility Study by FTIR

FTIR spectrum (Figure 2) of Trandolapril showed the peaks at 3280.70 cm-1 due to Amine group N-H Stretching vibration, 2879.87 cm-1 C-H Stretching vibration, 1735.83 cm-1 and 1653.67 cm-1 due to C-O Stretching vibration in ester, and amide groups respectively, 1193.29 cm-1 represents C-O-C Stretching vibration. The minor difference compared to pure sample were observed in drug-excipient mixture spectrum (Figure 3) as 3280.32, 2877.79 cm-1, 1735.78 and 1654.07, 1193.06. The study confirmed the absence of chemical interaction between drug and excipient.

4.2 Drug- Excipient Dompatibility Study by XRPD

The similar peaks with higher intensity were observed as shown in Figure 4 for pure drug (Trandolapril) and Drug-excipient (1:1) mixture with very minor difference suggested the compatibility of drug with inactive ingredients used in the formulation.

4.3 Pre-Compression Characteristics

The formulation blends initially were evaluated for pre-compression characteristics and results are shown in Table 2. The bulk density of the powder/s were in the range of 0.421±0.012 to 0.435±0.023 gm/ml; the tapped density was in the range of 0.478±0.001 to 0.492 gm/ml. Hausner's ratio were calculated and found the range of 1.11± 0.020 to 1.15±0.017 and the angle of repose of the formulations were in the range of 26.32º ±0.017 to 32.45º ±0.021 indicates good flow behavior of powder blends which indicated good flowability of the powder. The Carr's index was obtained in the range of 10.25±0.008 to 12.47±0.019 indicating good compressibility of the formulation blends.

4.4 Post- Compression Characterization of Tablets

As reported in Table 3, Average tablet weights were noted from 150.21±0.026 mg to 153.10±0.041 mg and all the formulations were within the %weight variation limit. Thickness of the tablets varied 0.59±0.002 to 0.62±0.008. The hardness was found within 4.3±0.026 to 5.2±0.021 kg/cm^2. Disintegration time varied between 30.23±0.069 to 71.67±0.071 seconds. Minimum disintegration was observed in formulation IRTR3 containing 6 % of crospovidone.

The drug content was obtained from 96.78±0.125 to 101.85±0.158, which was within the acceptable limits. Dissolution profiles of formulations IRTR1 to IRTR3, IRTR4-IRTR6 and IRTR7 to IRTR9 as shown in Figure 5. Percent cumulative drug release (%CDR) in 30 min for different batches was reported (Table 4) from 71.09± 0.275 to 90.56± 0.736. The maximum drug release was observed with IRTR3 containing crospovidone (90.56±0.736) among all formulations in 30 minutes.

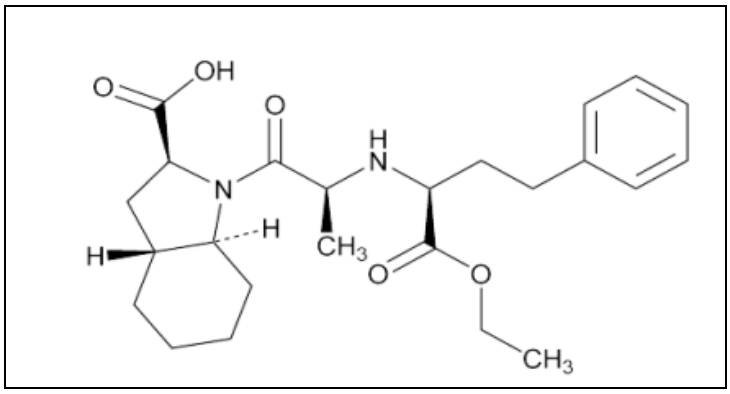

Figure 1: Structure of Trandolapril

Table 1: Formulation composition of Immediate release tablets of Trandolapril

Ingredients	IRTR1	IRTR2	IRTR3	IRTR4	IRTR5	IRTR6	IRTR7	IRTR8	IRTR9
Trandolapril	2	2	2	2	2	2	2	2	2
CP	3	6	9	-	-	-	-	-	-
SSG	-	-	-	3	6	9	-	-	-
CCS	-	-	-	-	-	-	3	6	9
MCC (PH 102)	50	50	50	50	50	50	50	50	50
Anhydrous Lactose	91	88	85	91	88	85	91	88	85
Magnesium stearate	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2
Total weight (mg)	150	150	150	150	150	150	150	150	150

CP: Crospovidone, SSG: Sodium starch glycolate, CCS: Croscarmellose sodium, MCC: Microcrystalline cellulose

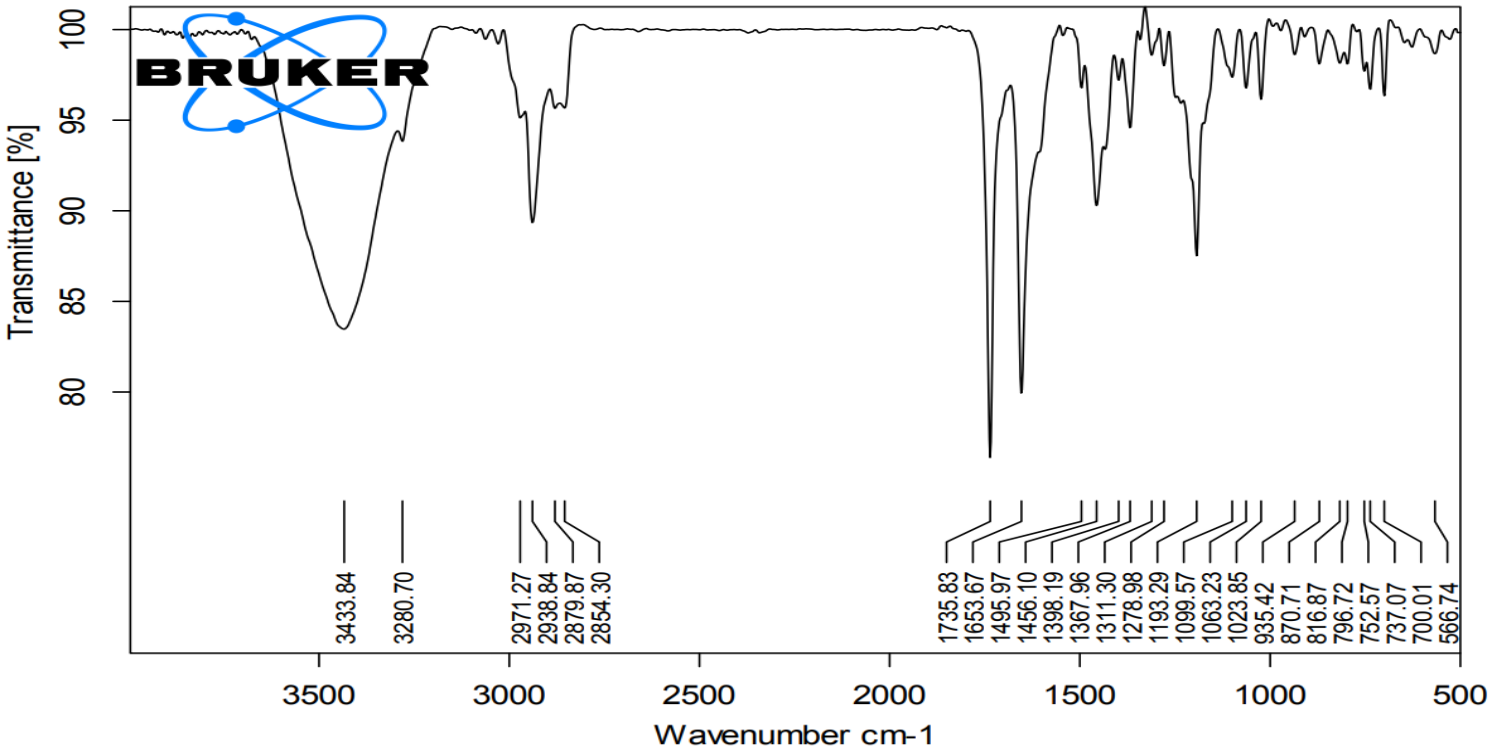

Figure 2: FTIR Spectrum of Pure Trandolapril

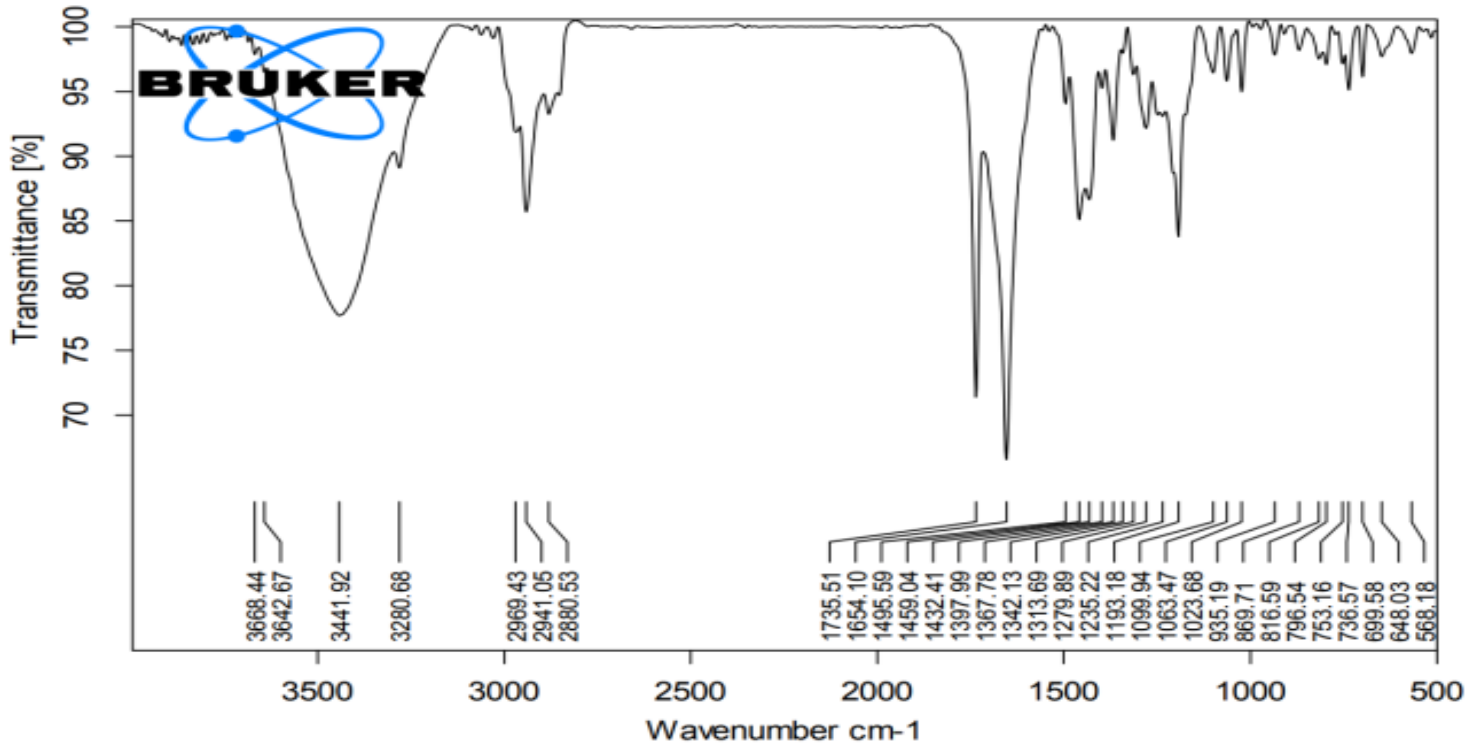

Figure 3: FTIR Spectrum of Trandolapril: Excipient mixture (1:1)

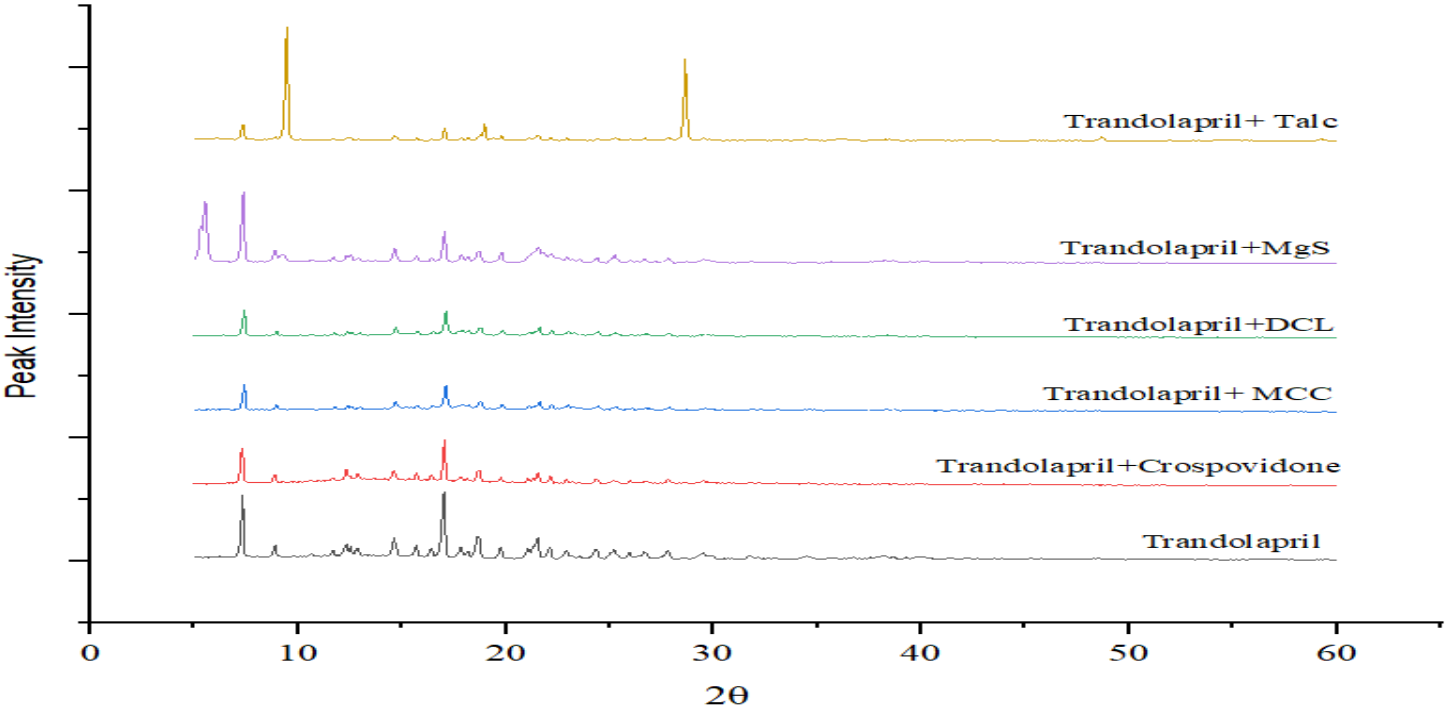

Figure 4: XRPD pattern of Trandolapril and (1:1); Trandolapril-Excipient (Crospovidone, MCC- Microcrystalline cellulose, DCL- Directly compressible lactose, MgS- Magnesium stearate, Talc)

Table 2: Evaluation of Pre- compressed Powder Blend

Formulation	Bulk density (mean± SD) (n=3)	Tapped density (mean± SD) (n=3)	Hausner's ratio (mean± SD) (n=3)	Carr's index (%) (mean± SD) (n=3)	Angle of repose (°) (mean± SD) (n=3)
IRTR 1	0.421±0.012	0.481±0.027	1.14±0.006	12.47±0.019	31.09±0.017
IRTR 2	0.422±0.014	0.485±0.018	1.15±0.017	12.99±0.013	32.45±0.021
IRTR 3	0.435±0.023	0.490±0.016	1.13±0.019	11.22±0.021	30.23±0.012
IRTR 4	0.431±0.021	0.492±0.013	1.14±0.026	12.40±0.012	31.54±0.016
IRTR 5	0.430±0.015	0.488±0.024	1.13±0.014	11.89±0.014	30.67±0.023
IRTR 6	0.427±0.027	0.484±0.016	1.13±0.033	11.78±0.007	30.23±0.014
IRTR 7	0.428±0.018	0.489±0.015	1.14±0.012	12.47±0.016	31.07±0.026
IRTR 8	0.426±0.024	0.482±0.012	1.13±0.041	11.62±0.005	30.45±0.028
IRTR 9	0.429±0.019	0.478±0.011	1.11±0.020	10.25±0.008	26.32±0.017

Table 3: Post-Compression characteristics of Immediate Release Tablet of Trandolapril

Formulation	Thickness (mm) (mean± SD) (n=10)	Hardness (kg/cm2) (mean± SD) (n=5)	Tablet weight (mg) (mean± SD) (n=20)	Drug content (%) (mean± SD) (n=3)	Disintegration time (Sec.) (mean± SD) (n=6)
IRTR 1	0.59±0.002	4.6±0.049	150.21±0.054	98.27±0.304	60.13±0.081
IRTR 2	0.61±0.007	5.0±0.071	152.13±0.036	99.26±0.149	34.45±0.063
IRTR 3	0.62±0.004	4.8±0.085	153.10±0.041	100.05±0.126	30.23±0.069
IRTR 4	0.61±0.003	4.9±0.046	151.36±0.014	96.15±0.232	68.12±0.016
IRTR 5	0.62±0.002	4.5±0.055	153.11±0.083	98.52±0.170	48.26±0.094
IRTR 6	0.62±0.001	5.2±0.021	152.14±0.024	98.48±0.188	39.56±0.081
IRTR 7	0.61±0.102	4.6±0.045	151.32±0.048	96.78±0.125	71.67±0.071
IRTR 8	0.61±0.007	4.3±0.026	152.40±0.061	98.25±0.175	56.32±0.034
IRTR 9	0.62±0.008	4.7±0.087	153.09±0.067	101.85±0.158	51.45±0.081

Table 4: % Cumulative drug release profiles of formulation (IRTR1 –IRTR13)

Time (min)	Cumulative % release of Trandolapril (mean±SD) (n=3)								
	IRTR 1	**IRTR2**	**IRTR3**	**IRTR 4**	**IRTR 5**	**IRTR 6**	**IRTR7**	**IRTR 8**	**IRTR 9**
0	0±000	0±000	0±000	0±000	0±000	0±000	0±000	0±000	0±000
5	45.68±0.456	49.47±0.538	50.87±0.583	34.23±0.506	38.15±0.176	42.23±0.506	39.02±0.183	40.62±0.178	45.71±0.043
10	56.82±0.378	61.10±0.915	65.12±0.824	52.35±0.011	61.15±0.014	63.54±0.109	49.47±0.53	53.47±0.672	57.47±0.487
20	65.09±0.675	70.12±0.325	76.05±0.427	64.33±0.834	69.13±0.384	71.33±0.870	56.82±0.220	64.82±0.560	70.96±0.329
30	80.36±0.789	84.21±0.609	90.56±0.736	74.56±0.922	78.34±0.220	82.56±0.832	71.09±0.275	76.19±0.382	80.45±0.632

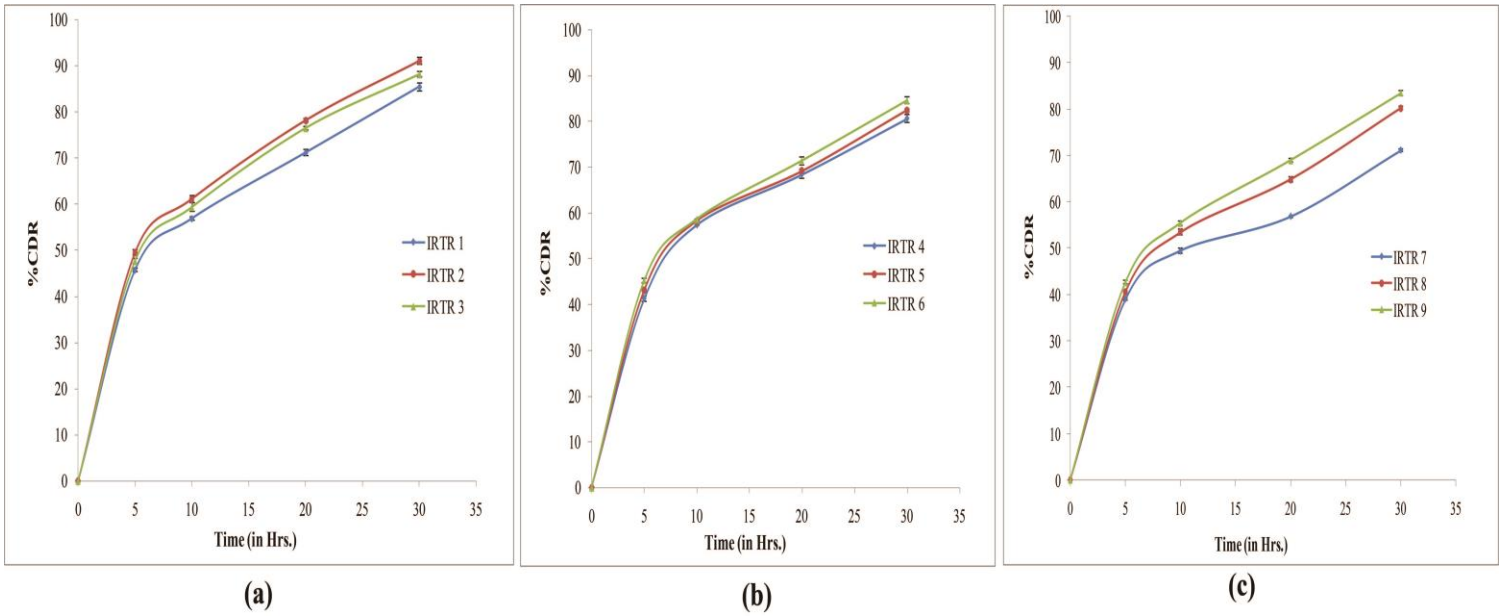

Figure 5: Dissolution profiles of formulations (a) IRTR1-IRTR3 (b) IRTR4-IRTR6 (c) IRTR7- IRTR9

5. CONCLUSION

All formulations were found to be satisfactory when evaluated for various quality control parameters. On the basis of minimum disintegration time and maximum drug release (more than 85%) formulation IRTR 3 was optimum for development of the Trandolapril immediate release tablets. The tablet disintegration time (30.23±0.069 seconds) was reported minimum with IRTR3 among the all tablet formulations. The percent cumulative drug release was found 90.56±0.736 in 30 min for IRTR3. The crospovidone was found most effective superdisintegrating agent in 6% concentration for the formulation of immediate release tablets of Trandolapril.

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