

Effects of superdisintegrants in oral dissolving formulation of cinitapride tablets

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Abstract: The initiation of newer techniques and development of mouth dissolving (MD) products has created new avenues of higher patients' compliance. MD formulations actually lessen the difficulties associated with solid swallowing with better bioavailability of especially poorly soluble drugs. In the current study mouth dissolving tablet (MDT) formulations of cinitapride (1 mg) were prepared by direct compression method using various proportion and combination of superdisintegrants. Nine formulations in three batches were compressed by incorporating low (2%), intermediate (6%) and higher (10%) levels of crospovidone, croscarmellose sodium, sodium starch glycolate. Micromeritic assessment of the powder blends were carried out and were found within the acceptable official limits. All newly developed trial formulations were exposed to different pharmacopoeial and non-pharmacopoeial testing. It was found that FC2 trial tablets containing polyplasdone XL[®] (crospovidone) at level of 6% (4.5 mg) presented the best physico-chemical attributes deemed to be desirable for the ODT products. Disintegration and wetting time of optimized FC2 was computed between 15-17 and 12-15 seconds respectively. The assay and content uniformity of FC2 were estimated to be 100.02±0.36 and 99.66±1.70 percent correspondingly. On the basis of the findings it was concluded that MDT could be successfully developed by incorporating appropriate concentration of superdisintegrant and their combinations.

Keywords: Mouth dissolving tablets, cinitapride, micromeritic assessments, formulation characterization.

INTRODUCTION

A significant proportion of the world's population experience problem in swallowing (dysphagia) pills, among them geriatric and paediatric patients are at the top of list (Tho, I., 2012; Radke *et al.*, 2009). The problem of dysphagia is not only due to fright of blocking in a throat but could also be possible due to certain pathogenic condition like tremors, and problem of muscular or nervous system in patients with schizophrenia (Gohel *et al.*, 2005; Bhagwati *et al.*, 2009). Orally disintegrating tablets (ODTs) provide an alternative to overcome these challenges. They resemble a traditional tablet but actually able to disintegrate rapidly in the mouth within few seconds without gulping hence greatly increases the consumers' compliance (Nagar *et al.*, 2011; Patel *et al.*, 2010). Although the disintegration time of ODTs is usually set to be within one min but usually these tablets are de-aggregated between 5-30 seconds (Kaur *et al.*, 2011). Superdisintegrants are the main adjuvant of such tablet formulations facilitating the fast dispersion of active and inert ingredients in buccal cavity (Comoglu *et al.*, 2016). Certain factors play a significant role in selection of superdisintegrants and their proportion. tablet hardness, kind of mixing, drug nature, flowability, compactability to formulate less friable tablets and

palatability are reported to be the critical factors (Kasliwal *et al.*, 2011). Orally disintegrating tablet engrosses the various mechanisms to accomplish the desirable quick dissolving features. ODTs wrecked down into the minor subdivision state of particles and consequently form fine dispersion, suspension or solution (Velmurugan and Vinushitha, 2010). Properties of some most popular superdisintegrants have been summarized in table 1 (Mangal *et al.*, 2012; Khan *et al.*, 2016).

Cinitapride, the selected drug for this study belongs to the benzamide class documented to be a gastro-prokinetic mediator and possesses anti-ulceratic properties. Chemically it is defined as 4-amino - N-[1-(1-cyclohex-3enylmethyl)-4-piperidyl]-2-ethoxy-5-nitro-benzamide. It is yellow crystalline in nature freely soluble in organic solvents including chloroform, methanol while soluble in water (Robert *et al.*, 2007). It has been widely prescribed all over the world to treat functional dyspepsia with safety and tolerance (Du *et al.*, 2104; Baqai *et al.*, 2013).

In the present study the mouth dissolving cinitapride tablets were developed using various concentrations of superdisintegrants. Direct compression technique was used to compress the trial formulations. Optimized tablet formulation was evaluated on the basis of satisfactory characterizing parameters including weight uniformity, hardness, friability, disintegration, wetting time, dissolution, content uniformity and assay.

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MATERIALS AND METHODS

Instrumentation

Digital analytical balance (Sortorius, Japan), Ultrasonic cleaner (Elma; America), Vernier Caliper (Seiko, China), Friability Tester (Curio FB 2020, Pakistan), tablet Hardness Tester Model PTB111E (Pharma test, Germany), Distillation Assembly (PLT, Genristo Ltd.), Magnetic stir, USP dissolution apparatus II (DA 6D, Veego, India), pH meter (Mettler Toledo, Switzerland) and UV-visible spectrophotometer, model UV 1800 (Shimadzu, Japan) with 1cm matched open top UV quartz cells

Chemicals/reagents

Cinitapride hydrogen tartrate (API), working standard and excipients (mannitol granules, sodium crosscarmellose (ac-di-sol), aspartame, microcrystalline cellulose (avicel PH102), sodium starch glycolate (primogel), crosspovidone (polyplasdone XL[®]), mint flavour and magnesium stearate were gifted by AGP Limited, Karachi Pakistan. Hydrochloric acid (Merck KGaA Darmstadt 6427 Germany) of analytical grade was procured from the commercial market.

Software

Microsoft Office[®] and statistical software SPSS 17.0 (SPSS Inc.) were used to analyze the data.

Methodology

Development and Optimization of orally disintegrating cinitapride (1mg) tablets

Orally disintegrating tablet of cinitapride were developed and optimized using three levels of three different superdisintegrants. In total, nine trial formulations, three from crosspovidone (FC1-FC3), three from crosscarmellose sodium (FM1-FM3) and three from sodium starch glycolate (FS1-FS3) were developed. Tablets were manufactured by direct compression method using 2%, 6% and 10% concentration of superdisintegrants, cinitapride hydrogen tartrate 1.373mg, mannitol granules (10 to 90%), microcrystalline cellulose PH 102 avicel (20-50%), Colloidal silicon dioxide aerosil-200 (0.1-0.5%), aspartame (2%), mint flavour and magnesium stearate (0.25-5.0%). Formulation composition of three batches is given in table 2. Ingredients were weighed accurately and passed from sieve with mesh aperture 20-mesh. Mixing of each powder blend was carried out in separate polybag manually by tumbling. Single punch tablet machine was used to compress all formulation runs.

Assessment of powder blends

Bulk and tapped densities

For bulk density determination, 10 g of powder blend was taken and the volume occupied was measured. For the assessment of tapped density, change in volume was noted down after the graduated cylinder was tapped 100

times and has shown no further decrease was observed in volume:

$$\text{Poured Bulk Density} = \frac{\text{Mass of Powder}}{\text{Bulk volume}} \quad (1)$$

$$\text{Tapped Bulk Density} = \frac{\text{Mass of Powder}}{\text{Tapped volume}} \quad (2)$$

Compressibility index

Carr's index and Hausner's ratio were determined to estimate the compressibility of the formulation runs. Following mathematical expressions were used (USP, 2012):

$$\text{Carr's Index} = 100 \frac{\text{Tapped bulk density} - \text{Poured bulk density}}{\text{Tapped bulk density}} \quad (3)$$

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \quad (4)$$

Angle of repose

Funnel method was used to calculate the angle of repose (Davies, 2001). Angle of repose was evaluated as:

$$\theta = \tan^{-1} = h/r \quad (5)$$

Whereas:

θ = Angle of repose in degrees

h = heap height

r = heap radius

Physico-chemical evaluation of orally disintegrating tablets

Weight variation test

For weight variation test twenty tablets were selected randomly from each trial formulation and their average weight was determined.

Acceptance limit

Not more than two tablets differ from the average weight by greater than the percentage mention in British and United state pharmacopoeias (B.P, 2017; USP, 2012).

Thickness variation

Twenty tablets were selected at random and their thickness was determined separately using digital Vernier calliper. Results were presented in mean and standard deviation.

Acceptance limit

Average diameter and thickness of 20 tablets should be in $\pm 5\%$ range (USP, 2012).

Assessments of hardness variation

Hardness test were carried out on twenty tablets individually, selected at random using digital hardness tester.

Acceptance limit

The preferable hardness for disintegrating tablet was reported to be in between 3-8kg (Liu *et al.*, 2002).

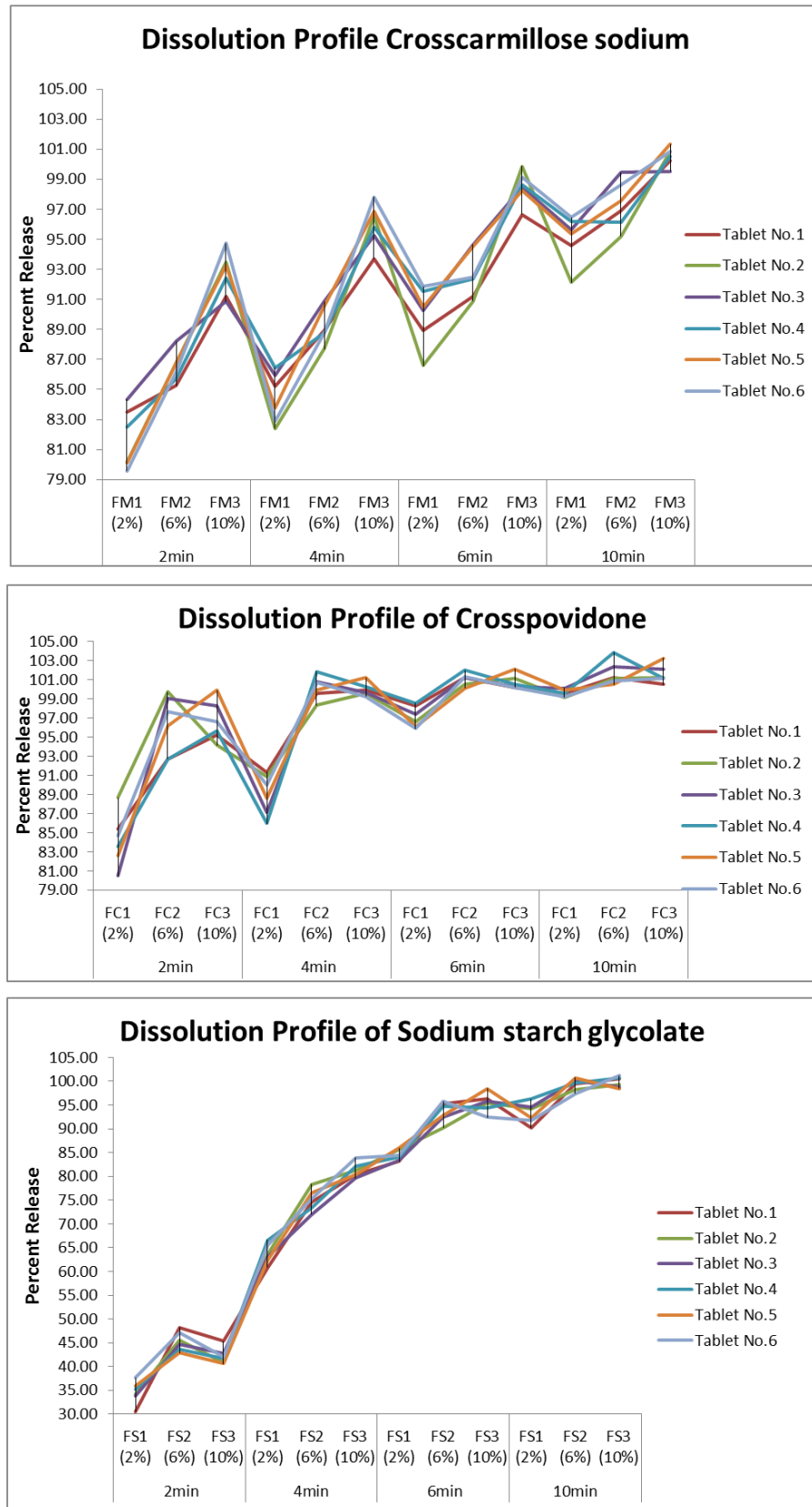


Fig. 1: Dissolution profile of mouth dissolving cinitapride trial formulations (FC1-FC3, FM1-FM3 and FS1-FS3)

Table 1: Properties of Super-disintegrant (Mangal *et al.*, 2012; Khan *et al.*, 2016)

Synthetic superdisintegrant	Characteristics	Effective range of concentration
Crospovidone Polyplasdone XL [®]	Quickly swelling and dispersibility in water. Highest degree of swelling. Superior surface area to volume ratio. Insoluble in water. Micronized forms are also available to facilitate the fine state of dispersion. Index of Swelling is 58±1.5% v/v; w/v.	1-3% w/w.
Croscarmellose Sodium Ac-Di-Sol [®]	Poor water solubility but higher degree of swelling up to 4-8 times of its initial volume. Values of surface area (Specific): 0.81-0.83 m ² /g. while swelling index is reported 65±1.7% v/v	5% w/w, in general, with 2 % w/w for direct compression and 3 % w/w for wet granulation procedure.
Sodium starch Glycolate Primojel [®]	Higher water Absorption, with 6% swelling capacity. High medication produces gelling and failure of disintegration process occurs. Swelling index- 52±1.2% v/v.	4-6%. beyond 8%, the time of disintegration increases because of gelling and subsequent raise in viscosity

Table 2: Formulation composition of Cinitapride OTD Tablets with Batch Codes

Formulation Batches	Batch Code	Poured Bulk Density	Tapped Density	Angle of Repose	Hausner's ratio	Compressibility Index
Batch I	FC1	0.4377	0.5135	26.75	1.173	14.76
	FC2	0.4339	0.5097	27.15	1.174	14.88
	FC3	0.4317	0.5233	27.89	1.212	17.50
Batch II	FM1	0.4463	0.5193	31.04	1.164	14.04
	FM2	0.4520	0.5350	31.79	1.184	15.50
	FM3	0.4326	0.5053	32.46	1.168	14.38
Batch III	FS1	0.4613	0.5602	31.04	1.214	17.65
	FS2	0.4496	0.5510	31.79	1.226	18.40
	FS3	0.4409	0.5150	28.64	1.168	14.38

Table 3: Comparative study of Pre-formulation Parameters of Batch I, II, & III

Batch Codes	Batch-I			Batch-II			Batch-III		
	FC1	FC2	FC3	FM1	FM2	FM3	FS1	FS2	FS3
Ingredients (mg)									
Cinitapride Hydrogen Tartrate	1.375	1.375	1.375	1.375	1.375	1.375	1.375	1.375	1.375
Mannitol granules	42.5	39.5	36.5	42.5	39.5	36.5	42.5	39.5	36.5
Microcrystalline cellulose PH 102	26.25	26.25	26.25	26.25	26.25	26.25	26.25	26.25	26.25
Crospovidone	1.5	4.5	7.5	-	-	-	-	-	-
Croscarmellose Sodium	-	-	-	1.5	4.5	7.5	-	-	-
Sodium Starch Glycolate	-	-	-	-	-	-	1.5	4.5	7.5
Colloidal Silicon dioxide	0.375	0.375	0.375	0.375	0.375	0.375	0.375	0.375	0.375
Aspartame (sweetener)	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Mint Flavor	0.375	0.375	0.375	0.375	0.375	0.375	0.375	0.375	0.375
Magnesium Stearate	1.125	1.125	1.125	1.125	1.125	1.125	1.125	1.125	1.125
Total weight of tablet (mg)	75.00	75.00	75.00	75.00	75.00	75.00	75.00	75.00	75.00

Friability test

Roche Friabilator was used to perform the friability test using 25 rpm for 4 min.

Acceptance limits

According to USP, for conventional tablets, % friability should be < 1% (USP, 2012).

Test for finess of dispersion

Two tablets were placed in 100mL beaker containing water and then mix until both tablets were uniformly dispersed. Pour this dispersion through 710µm mesh sieve.

Acceptance limits

Dispersion should be able to pass through 710µm mesh aperture (BP 2017).

Table 4: Physico-chemical Characterization of Cinitapride trial ODT Formulations

Formulation Batches	Batch Code	Weight ^a (mg) ±SD	Thickness ^b (mm) ±SD	Hardness ^b (kg) ±SD	Friability (%)	Disintegration Time (Seconds)	Wetting time ^b (Seconds)	Assay contents	Content Uniformity
Batch I	FC1	75.54±1.01	2.738±0.23	4.63±7.82	0.132	27-31	32 - 36	99.96±0.38	99.93±1.87
	FC2	75.98±0.84	2.736±0.46	3.63±2.92	0.152	15-17	12. - 15	100.02±0.36	99.66±1.70
	FC3	75.83±1.14	2.739±0.32	2.59±13.9	0.439	12-15	10. - 12	100.60±0.42	99.88±2.06
Batch II	FM1	75.74±1.00	2.780±0.29	4.45±8.56	0.116	48-53	48 - 52	100.49±0.18	99.94±2.01
	FM2	75.89±0.92	2.781±0.31	2.90±4.60	0.158	28-32	20 - 22	100.31±0.33	99.40±1.70
	FM3	75.83±0.65	2.781±0.27	2.65±7.17	0.405	18-21	14 - 16	100.45±0.53	100.15±1.56
Batch III	FS1	75.47±0.72	2.752±0.23	4.84±5.44	0.108	75-85	55 - 60	100.78±0.64	99.98±2.33
	FS2	76.02±0.60	2.753±0.25	3.57±6.60	0.153	55-63	48 - 52	100.48±0.52	99.21±1.70
	FS3	75.66±1.02	2.750±0.30	2.82±6.43	0.369	45-52	40 - 42	100.58±0.30	99.83±2.44

Disintegration test

Six tablets of each formulation were placed in basket rack assembly with perforated disks. The test was conducted in water at 15°C to 25°C at 37°C±2°C (USP, 2012)

Acceptance limits

The time of disintegration for ODT is less than 30 seconds (FDA, 2008).

Determination of wetting time

A piece of twice folded tissue paper was placed in a 6.5 cm petri dish containing 6mL of pH 6.75 (simulated saliva fluid) (Jacob *et al.*, 2007). Single tablet was placed in petri dish over the paper and period for absolute wetting was calculated.

Acceptance limits

The wetting time for orally disintegrating tablet is less than 30 seconds.

Assay test

Twenty tablets were weighed individually and then crushed. The amount equal to average weight of tablet was taken in 100mL volumetric flask, 20mL 0.1N HCl was added as diluent to prepare 0.01mg/mL concentration. Similarly cinitapride hydrogen tartrate working standard solution having identical strength was prepared. The absorbance of both solutions was determined at 266nm (Rehman, A *et al.*, 2017).

Acceptance limits

The acceptance limits is 95%-105%.

Content uniformity test

Ten samples for content uniformity were prepared by taking one tablet in 100mL volumetric flask followed by the addition of 20mL 0.1N HCl. Mixture was sonicated for 5 minutes with volume making. Cinitapride hydrogen tartrate working standard solution having the same concentration was also prepared. The absorbance of both solutions was determined at 266nm wavelength (Rehman, A *et al.*, 2017).

Acceptance limits

The acceptance limits of Content uniformity of tablets in B.P are 85%-115% (B.P, 2017).

Dissolution test

The percentage (%) drug release of nine different formulations of cinitapride (F1-F9) was estimated using USP apparatus (II) at a speed of 50 rpm. 500mL of 0.1N HCl was utilized as a medium maintained at 37±0.5°C for 2, 4, 6 and 10 minutes. The percentage drug release was analyzed by UV spectrophotometer at 266 nm wavelength.

Acceptance limits

Not less than 85 % in 10 minutes (Abay, F.B. and Ugurlu, T., 2015).

RESULTS

In this study various mouth dissolving formulations of cinitapride were developed using various concentrations

of superdisintegrants including primojel[®], ac-di-sol[®] and polyplasdone XL[®] as shown in table 2. Model drug was selected due to unavailability of mouth dissolving formulation of cinitapride in the local market of Pakistan. Trial formulations were developed utilizing different compositions of mannitol granules and superdisintegrants while cinitapride, avicel PH102, aspartame, mint flavour, magnesium stearate and colloidal silicon dioxide were kept at a fixed concentration as given in table 2. Flow characteristics of different formulations FC1-FC3 (containing croscopolvidone), FM1-FM3 (containing croscarmellose sodium) and FS1-FS3 (containing sodium starch glycolate) were assessed by different equations including bulk and tapped density (Eq. 1 & 2), Carr's index (Eq. 3), Hausner's ratio (Eq. 4) and angle of repose (Eq. 5). Values of these parameters are summarized in table 3.

Since all formulations have shown the acceptable micromeritics properties hence subjected to direct compression for tablet manufacturing. Various physico-chemical testing were performed for the determination of pharmaceutical quality of compressed tablets. All the formulations (FC1-FC3, FM1-FM3 and FS1-FS3) were compressed having thickness within the recommended range of $\pm 5\%$. Dissolution pattern of these formulations was presented in fig. 1. Results of compressional testing parameters are summarized in table 4.

DISCUSSION

Tablets are the extensively used dosage forms due to its ease for self administration, solidity and alleviated way of manufacturing. A considerable difficulty in swallowing a conventional formulation of tablet has been reported in literature specifically to pediatric and geriatric population (Shimizu *et al.*, 2003). "Melt in mouth" or "oral disintegrating" and "mouth dissolving" (MD) tablets are mostly answer such difficulties faced by these patients as they instantly release the active constituents of enclosed drug, when positioned on the tongue, by quick disintegration and dissolution of the medicine (Dave *et al.*, 2015; Kundu and Sahoo, 2008). Mouth dissolving tablets offer the benefit of liquid and solid formulations altogether and support the comfortable swallowing of drug ingredients in the solution form (Bandari *et al.*, 2008; Qureshi *et al.*, 2017).

Moreover, an elevated tendency towards the manufacture of reasonably priced generic formulation has attained noteworthy interest globally (Cameron, 2009). Researchers, health agencies and drug authoritarian groups in conjunction with manufacturer as well authorize the comparable therapeutic effectiveness of newly produced drug moieties as like pacesetter. Incidentally a variety of new dosage forms are explored that are not only cost efficient, but simultaneously proficient in terms of

required quality aspects (Maroof *et al.*, 2016). In present work mouth dissolving tablet formulations were designed and then compressed by means of direct compression (DC) procedure. DC is a realistic and expedient technique to produce tablets with fundamental properties and virtues in most reliable and affordable manner (Sri *et al.*, 2012; Ali *et al.*, 2013, Bushra *et al.*, 2014). Therefore in current investigation blends of cinitapride were compressed by direct compression method using active drug component, directly compressible constituents, superdisintegrants, flavouring and sweetening agents. Earlier many researchers have used mannitol as base for orally disintegrating tablets (Sunada and Bi, 2002).

Prior to the compression the micromeritic assessment of powder blends was carried out. The poured bulk and tapped densities (Eq. 3-4) of the trial formulations (FC1-FC3, FM1-FM3 and FS1-FS3) were correspondingly in the order of 0.4317-0.4613; 0.5053-0.5602g/mL. The angle of repose of these formulations was found to be 26.75-32.46^o. These angle values of indicates the better flowing behaviour of these formulations and less cohesive pattern during process of tableting. The Hausner's ratio of all formulations was in the range of 1.164-1.226, which was less than 1.25 and designates acceptable flow characters of formulation. The Carr's index was found between 14.04-18.40% the lowest with FM1 as presented in table 3. Performance of powder flow distinctiveness is among the major parameters for the improvement and design of different pharmaceutical dosage form predominantly for tablets. Researchers investigated the flow pattern of different formulation in order to optimize the compression and flow characteristics (Qureshi *et al.*, 2017). An exceptional association was reported amongst the pharmaceutical quality and tablets substance (active and excipients). Researchers reported the indirect association between the concentration of Avicel PH-102 and angle of repose, i.e., higher the concentration of Avicel, steeper the values of corresponding angle (Bolhuis and Armstrong, 2006).

In this study outcome of thickness, weight variation, and hardness variations of formulations (FC1-FC3, FM1-FM3 and FS1-FS3) were observed to be in the range of 2.736 \pm 0.46-2.781 \pm 0.31 mm; 75.47 \pm 0.72-76.02 \pm 0.60 mg, 2.59 \pm 13.9-4.84 \pm 5.44 kg respectively (Table 4). Variation weight is frequently due to the diverged flow description of the corresponding blends which may lead to the unseemly filling of die cavity. Likewise, tablet hardness is a competent marker of the binding aspect of the filler-binder and the functional compressional strength over which powder mixtures have been compacted (Muhammad *et al.*, 2012). In the same way, Lahdenpaa *et al.*, premeditated that elevated proportion of avicel PH-102 augment the levels of crushing strength of successive formulations (Lahdenpaa *et al.*, 1997).

Correspondingly % friability and disintegration time of mouth dissolving tablet were found to be in the range of 0.108-0.439 % and 12-85 seconds presented in Table 4. Range of disintegration test for (FC1-FC3, FM1-FM3 and FS1-FS3) were found to be 12-15 to 27-31 seconds; 18-21 to 48-53 and 45-52 to 75-85 seconds. Superdisintegrants are the elementary components enclosed in ODT and are accountable for their exclusive facilitation for tablets to swiftly break up and dissolve over the exterior of the tongue with no use of any extra liquid. In this work three superdisintegrants were tested, namely: primojel[®] (sodium starch glycolate), ac-di-sol[®] (crosscarmillose sodium), and polyplasdone XL[®] (crosspovidone), with the intention to select the most proficient superdisintegrant for ODT formulation. polyplasdone XL[®] has produced outperformed results in contrast to other superdisintegrants with excellent quality attributes over others. Levels of 6% polyplasdone XL[®] has given the most desirable outcomes. Furthermore, all formulations (FC1-FC3, FM1-FM3 and FS1-FS3) pass the finess of dispersion test. The percentage (%) drug release of nine different formulations of cinitapride was estimated using USP apparatus (II) at a speed of 50 rpm. For this purpose 500mL of 0.1N HCl was utilized as a medium at 37±0.5°C for 2, 4, 6 and 10 minutes (fig. 1). Results demonstrated the insignificant variation between release pattern batch I and II, while noteworthy variation in Batch III was observed. The percentage drug release was analyzed by UV spectrophotometer at 266 nm wavelength. Wetting time of these formulations was observed in the range of 10-12 and 48-52 seconds respectively. On the basis of wetting time FC2-FC3, FM2-FM3 pass the test i.e., within 30 seconds. While, batch III of FS1-FS3 doesn't comply the specifications (table 4). In another study, investigators assessed the association of wetting time and concentration of crosopvidone. Wetting and disintegration time was found to be decreased with higher concentration of superdisintegrants (Nawale and Mohite, 2013). Similarly, results of content uniformity and assay estimation were consecutively found in the range of 99.21±1.70-100.15±1.56% and 99.96±0.38-100.78±0.64% respectively (table 4). Recent developments in novel systems of drug-delivery are intended to improve the safety and effectiveness of the drug moieties and to design and formulate a conveniently administrable dosage form.

CONCLUSION

Dissimilar dosage forms necessitate special technologies to produce required pharmaceuticals and typically present diverse challenges related to technical and formulation aspects. Henceforth in current study, the determination of the most effectual category of superdisintegrants and optimal amount of other formulations additives for orally disintegrating tablets were investigated and then prepared

by direct compression technique. Furthermore all necessary tablet parameters were evaluated including thickness, hardness, friability, disintegration and wetting time, along with drug release behaviour and content uniformity. Results of all these parameters support the tablet formulation of mouth dissolving cinitapride. This study will be supportive in selection of various ratios of superdisintegrants for development of cinitapride tablets.

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