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FORMULATION AND EVALUATION OF ORAL DISPERSIBLE TABLETS OF ATENOLOL

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Conflicts of Interest: Nil

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ABSTRACT

Atenolol is a commonly used beta-blocker that is advocated for the treatment of hypertension. The Objective of the present work was to formulate and evaluate mouth dissolving tablets of Atenolol by selecting suitable taste masking agent and super disintegrants for better patient compliance. The availability of various technologies and the manifold advantages of ODT will surely enhance the patient compliance, low dosing, and rapid onset of action, fast disintegration, low side effect, good stability and its popularity in the near future. In the present work, oral dispersible tablets of Atenolol were prepared by direct compression method using three superdisintegrant namely Cross povidone, Croscaramellose sodium, sodium starch glycolate. All the tablets are subjected to drug content uniformity, hardness, friability, wetting time, water absorption ratio, disintegration, dissolution, drug excipients interaction and short-term stability studies.

Keywords: atenolol, CPS,SSG, povidone.

INTRODUCTION

The oral route of administration is considered as the most widely accepted route because of its convenience of self administration, compactness and easy manufacturing. But the most evident drawback of the commonly used oral dosage forms like tablets and capsules is difficulty in swallowing, leading to patients incompliance particularly in case of pediatric and geriatric patients[6], but it also applies to people who are ill in bed and to those active working patients who are busy or traveling, especially those who have no access to water.[1] Over a decade, the demand for development of orally disintegrating tablets (ODTs) has enormously increased as it has significant impact on the patient compliance. Orally disintegrating tablets are appreciated by a significant segment of populations particularly who have difficulty in Dysphasia (difficulty in swallowing) is common among all age groups and more specific with pediatric, geriatric population along with institutionalized patients ,psychiatric patients and patients with nausea, vomiting, and motion sickness complications. ODTs with good taste and flavor increase the acceptability of bitter drugs by various groups of population[2]

Orally disintegrating tablets are also called as orodispersible tablets, quick disintegrating tablets, mouth dissolving tablets, fast disintegrating tablets, fast dissolving tablets, rapid dissolving tablets, porous tablets, and rapimelts. However, of all the above terms, United States pharmacopoeia (USP) approved these dosage forms as ODTs. Recently, European Pharmacopoeia has used the term orodispersible tablet for tablets that disperses readily and within 3 min in mouth before swallowing.[3]

ODTs involve the following mechanisms to achieve the desired fast dissolving characteristics. Water must quickly enter into the tablet matrix to cause rapid disintegration and instantaneous dissolution of the tablet[4].

Incorporation of an appropriate disintegrating agent or highly water soluble excipients in the tablet formulation.

There are some under mentioned mechanisms by which the tablet is broken down into the smaller particles and then subsequently result a solution or suspension of the drug[5].

The present research involves formulation and evaluation of oral dispersible tablet of atenolol using three different superdisintegrant.

Materials and methods

Atenolol used as active drug, Cross povidone , Croscaramellose sodium and Sodium starch glucolate used as superdisintegrant, Micro crystalline cellulose used as diluents, Mannitol used

as sweeter and Talc, Magnesium Stearate used as lubricant.

Methods

Drug-excipients compatibility study by FTIR

FTIR study was done to verify if there was any interaction between the pure drug and various excipients were employed. The various FTIR graphs both of pure drug and optimization formula formulated into IR pellet and scanned

Formulation of tablet

Direct compression is the most common method employed for MDT preparations as it offers a number of advantages like ease of manufacturing, limited processing steps, etc.

Superdisintegrants Crospovidone, Croscarmellose Sodium, Sodium starch glycolate are used in different concentrations (2%,4%,6% of tablet weight) and mannitol as direct compressible vehicle. Tablets are compressed with 8mm diametric punches. The dose of drug taken is 50mg per 200mg tablet.

All tablet ingredients are weighed as per the compositions in table and triturated well in a mortar and passed through sieve no 80. The obtained powder blend was compressed using compression machine with 8mm round punch by direct compression technique. The tablet weight was maintained to 200mg. A minimum of 50 tablets were prepared for each batch.

Table 1: Formulation ingredients for all batches

Formulation ingredient	DC_1	DC_2	DC_3	DC_4	DC_5	DC_6	DC_7	DC_8	DC_9
Propranolol HCl	50mg	50mg	50mg	50mg	50mg	50mg	50mg	50mg	50mg
CPV	4mg	8mg	12mg	-	-	-	-	-	-
CCS	-	-	-	4mg	8mg	12mg	-	-	-
SSG	-	-	-	-	-	-	4mg	8mg	12mg
Mannitol	80mg	80mg	80mg	80mg	80mg	80mg	80mg	80mg	80mg
MCC	56mg	52mg	48mg	56mg	52mg	48mg	56mg	52mg	48mg
Aspartame	6mg	6mg	6mg	6mg	6mg	6mg	6mg	6mg	6mg
Talc	2mg	2mg	2mg	2mg	2mg	2mg	2mg	2mg	2mg
Magnesium stearate	2mg	2mg	2mg	2mg	2mg	2mg	2mg	2mg	2mg
Total	200mg	200mg	200mg	200mg	200mg	200mg	200mg	200mg	200mg

Evaluation of blended powder

Bulk density (B.D): It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder (passed through standard sieve # 20) into a measuring cylinder and the initial volume 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/cc and is given by[6]

$B.D = m/V_O$

Where,

m = mass of the powder

V_O = bulk volume of the powder

Tapped density (T.D): It is the ratio of total mass of powder to the tapped volume of powder. The volume was measured by tapping the powder for 500 times. Then the tapping was done for 750 times and the tapped volume was noted (the difference between these two volumes should be less than 2%). If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. It is expressed in g/cc and is given by[7]:

$T.D = m/V_i$

Where,

m= mass of the powder.

V_i = tapped Volume of the powder.

Hausner's Ratio (H.R) : It is measurement of frictional resistance of the drug. The Ideal range should be 1.2 – 1.5, it was determined by the ratio of tapped density and bulk density[8].

H.R = T.D / B.D

Compressibility Index (C.I): The flow ability of powder can be evaluated by comparing the Bulk

density (BD) and Tapped bulk density (TD) of powder and the rate at which it packed down. Compressibility index was calculated using the following formula[9];

C.I = 100 X (1 – 1/H.R.)

Angle of repose: Angle of repose is defined as the maximum angle possible between the surface of the pile of powder and the horizontal plane[10]

The angle of repose is designed by θ and given by equation

Tan θ= h/r or θ=$\tan^{-1}$ h/r

Evaluation of tablet

General appearance: The prepared tablets were evaluated visually for their appearance, texture and tablets defects.

Uniformity of weight (Weight variation test): 20 tablets were weighed individually and collectively. Average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight. The percentage difference in the weight variation should be within the permissible limits of 7.5% .

Hardness test: The hardness of a tablet is an indication of its strength. The tablet should be stable to mechanical stress during handling and transportation. The hardness was tested using Monsanto hardness tester. The average of the five determinations was determined and reported.

Friability test (F): 20 tablets were weighed collectively and placed in the chamber of the friabilator. In the friabilator, the tablets were exposed to rolling, resulting from free fall of tablets within the chamber of the friabilator. After 100 rotations (i.e. in 4 minutes), the tablets were taken out from the friabilator and intact tablets were again weighed collectively. Permitted friability limit is 1.0%. The percent friability was determined using the following formula:

$F = (W_1 – W_2)/W_1 \times 100$

Where,

W_1 = weight of the tablets before test

W_2 = weight of the tablets after test

Disintegration test: The in-vitro disintegration time was determined using disintegration test apparatus. A tablet was placed in each of the six tubes of the apparatus and one disc was added to each tube. The time in seconds taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured in seconds[11].

In -Vitro dispersion test: In-vitro dispersion time is measured by dropping a tablet in a beaker containing 50 ml of phosphate buffer pH 6.8. Three tablets from each formulation are randomly selected and in vitro dispersion time is carried out.

In-Vitro dissolution test: In-vitro dissolution study is performed by using USP Type II Apparatus (Paddle type) at 50 rpm. Phosphate buffer pH 6.8, 900 ml is used as dissolution medium which is maintained at 37±0.5°C. Aliquots of dissolution medium (10 ml) are withdrawn at specific time intervals (2 min) and filter. An equal amount of fresh dissolution medium is replaced immediately following withdrawal of test sample. A portion of sample was filtered and analyzed by a spectrophotometer (Shimadzu, Japan) at 225 nm .The percentage of drug released at various intervals is calculated using beer-lamberts law.

Assay: Twenty tablets were weighed and powdered. The blend equivalent to 25 mg of Atenolol was weighed and dissolved in sufficient quantity of PH 6.8 phosphate buffer. The solution was filtered through Whatmann filter paper (no.41), suitably diluted with pH 6.8 phosphate buffer and assayed at 224.2 nm, using a UV-Visible double beam spectrophotometer[12]

Stability study: Stability of a drug can be defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specifications. The best formulation of all the batches is subjected to stability study as per ICH guidelines to assess their stability with respect to their physical appearance and release characteristics. The stability studies are carried out as prescribed by ICH Q1A guidelines for which tablets are stored at 40±1°C/75%±5% RH for 4 weeks. The tablets are tested by wrapping them in aluminium foil and packed in glass vials. These tablets were kept in incubator and then were withdrawn after 4 weeks and analysed for physical characterization, visual defects, hardness, friability, disintegration test, dissolution tests

Result and discussion

FTIR study

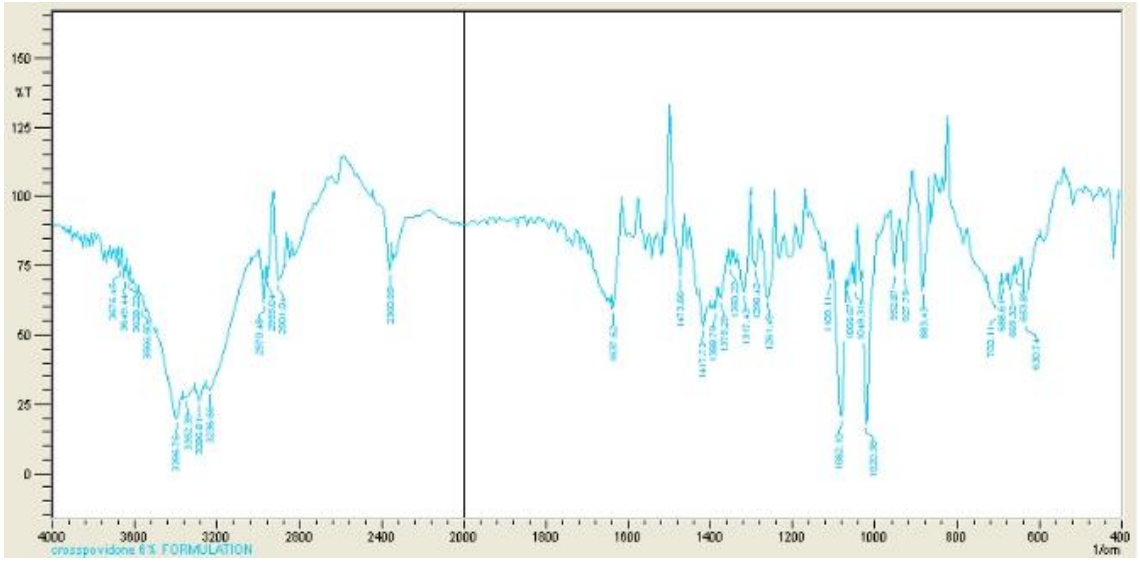

Fig. 1: IR spectra of Drug with Sodium Starch Glycollate

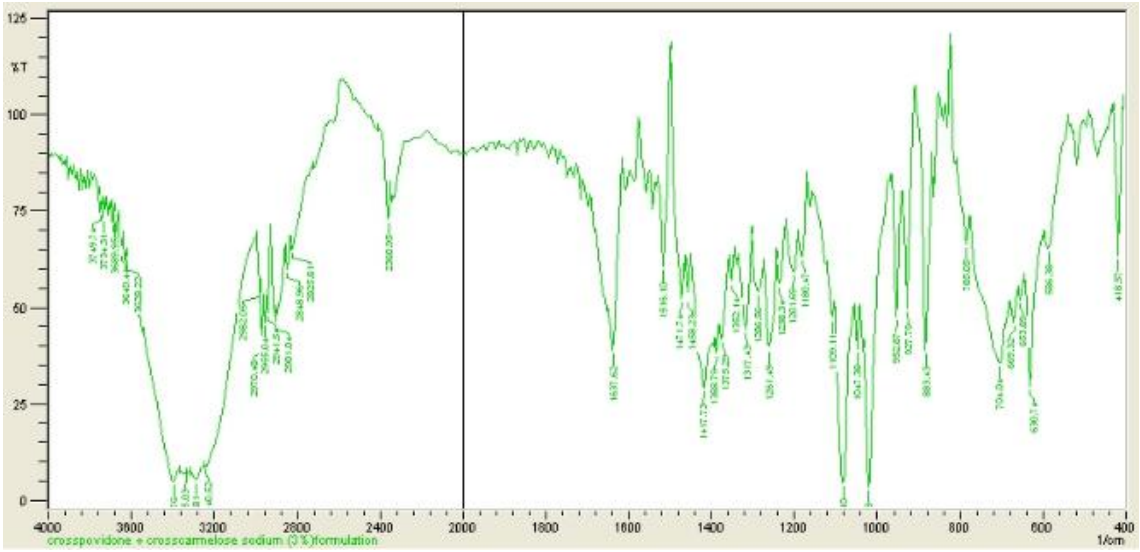

Fig. 2: IR spectra of drug with Cross Carmellose Sodium

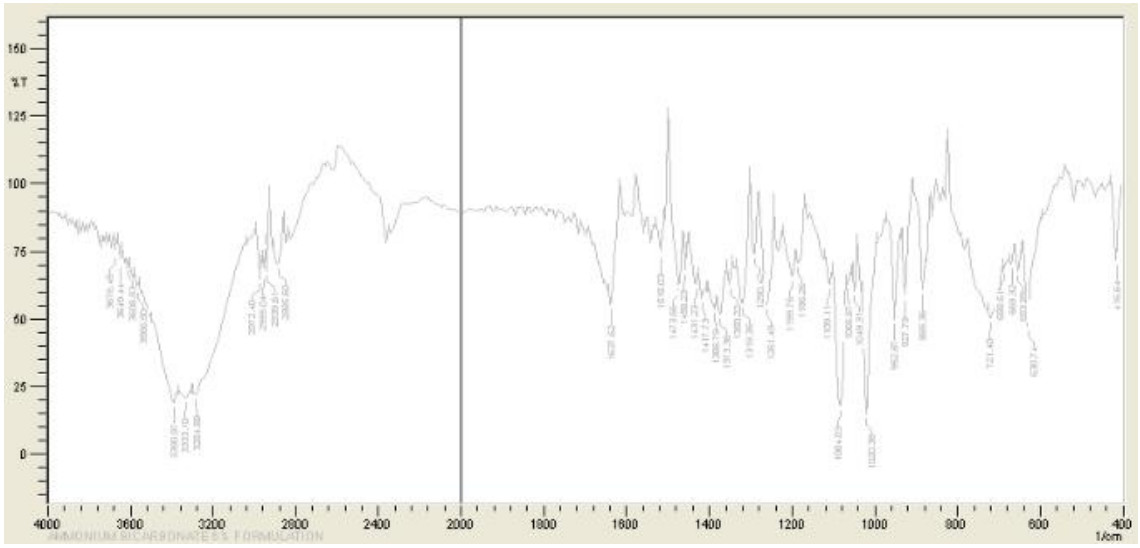

Fig. 3: IR spectra of drug with Cross Povidone

Result of evaluation of blended powder

Table 2: Evaluation of powder blend of direct compression method

Formulation code	Angle of repose(θ)	Bulk density (gm/cm^3)	Tapped density(gm/cm^3)	Hausner's ratio	Carr's index (%)
DC_1	31.08	0.528	0.692	1.31	23.699
DC_2	30.78	0.541	0.652	1.205	17.024
DC_3	31.92	0.530	0.614	1.158	13.68
DC_4	29.53	0.538	0.639	1.187	15.805
DC_5	29.62	0.512	0.621	1.21	17.55
DC_6	30.12	0.521	0.630	1.209	17.301
DC_7	28.17	0.543	0.640	1.178	15.156
DC_8	29.6	0.509	0.599	1.176	15.025
DC_9	30.09	0.534	0.682	1.27	21.70

Result of evaluation of tablet

Table 3: Evaluation of tablets prepared by direct compression method.

Formulation code	Weight variation	Hardness (in kg/cm^2)	Thickness (in mm)	Friability (%)
DC_1	0.202±2.97%	2.8±0.24	3.5	0.74%
DC_2	0.205±0.97%	2.9±0.16	3.5	0.66%
DC_3	0.202±0.99%	2.7±0.24	3.5	0.497%
DC_4	0.204±1.47%	2.9±0.12	3.5	0.496%
DC_5	0.201±0.99%	2.85±0.12	3.5	0.496%
DC_6	0.207±0.48%	2.9±0.16	3.5	0.664%
DC_7	0.202±1.98%	2.9±0.16	3.5	0.80%
DC_8	0.204±2.45%	2.7±0.24	3.5	0.827%
DC_9	0.203±1.47%	2.8±0.24	3.5	0.40%

Table 4: Evaluation of wetting time, water absorption ratio, disintegration time and drug content.

Formulation code	Wetting time (in sec)	Water absorption ratio(%)	Disintegration time(in sec)	Drug content(%)
DC_1	50±0.01	23.71±0.7	98.02±0.30	94.24
DC_2	44.66±1.77	23.315±2.42	90.12±1.53	95.68
DC_3	43.66±1.2	25.395±5.1	89.16±0.90	93.47
DC_4	58.66±1.10	19.36±1.02	117.20±1.33	94.24
DC_5	54.66±2.21	21.35±2.45	115.5±2.08	93.68
DC_6	54.66±1.10	22.59±2.93	102.34±0.88	96.47
DC_7	59.66±1.10	18.45±1.34	121.22±2.5	95.29
DC_8	56.33±0.87	21.743±2.25	117.23±1.15	95.29
DC_9	56.33±2.21	21.24±1.13	113.09±2.0	94.66

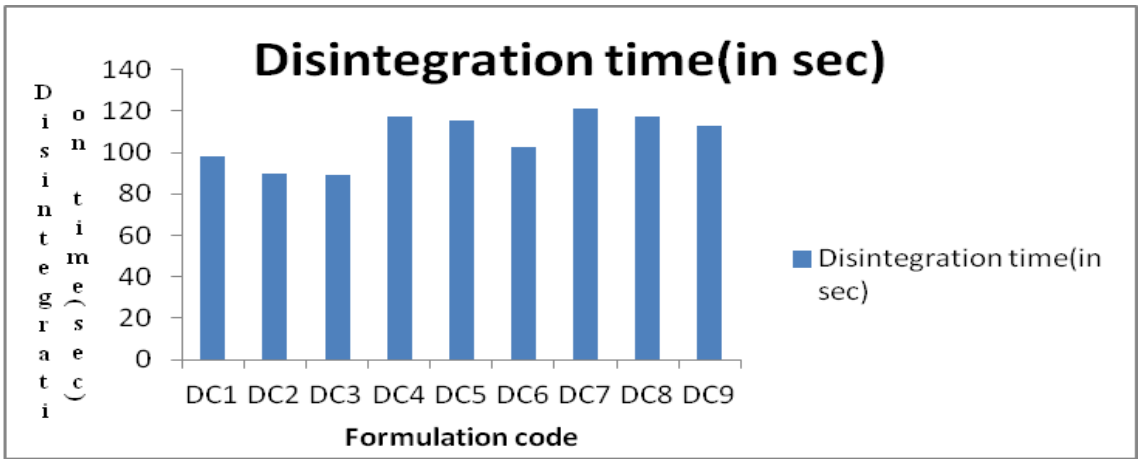

Fig. 4: disintegration time of all formulations

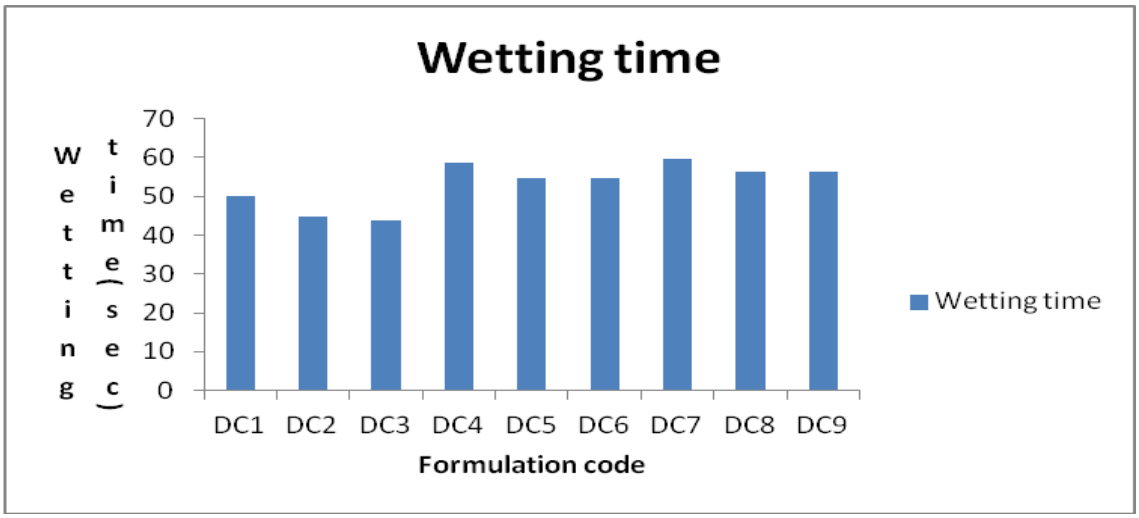

Fig. 5: Wetting Time of all formulations

Table 5: Cumulative percentage drug released from MDTs prepared by direct compression.

Time (in min)	DC_1 (2%CPV)	DC_2 (4%CPV)	DC_3 (6%CPV)	DC_4 (2%CCS)	DC_5 (4%CCS)	DC_6 (6%CCS)	DC_7 (2%SSG)	DC_8 (4%SSG)	DC_9 (6%SSG)
0	0	0	0	0	0	0	0	0	0
2	21.27	29.14	32.318	11.965	26.284	27.92	11.96	12.17	21.37
4	50.37	53.693	49.909	31.60	36.102	39.579	29.556	32.011	33.034
6	57.068	67.806	62.386	39.886	44.181	50.215	39.886	39.886	41.931
8	64.732	73.43	70.465	45.30	57.375	59.52	46.227	42.75	46.94
10	77.625	79.875	79.261	50.82	61.36	62.693	52.875	53.488	59.829
12	77.52	84.88	88.977	58.5	69.238	70.15	51.443	61.159	63.511
14	79.97	90	85.909	66.78	70.97	72.81	57.988	63.511	70.363
16	81.81	90.32	93.068	69.75	75.57	76.705	61.772	66.886	72
18	91.022	91.02	93.068	73.636	79.261	80.181	65.352	71.59	76.909
20	92.113	93.54	94.09	77.11	81.61	82.86	68.420	74.25	80.59
22	92.223	95.09	94.78	79.465	82.943	88.05	72.715	75.57	82.227
24	93.67	95.72	96.56	84.80	91.344	93.156	85.090	83.70	87.373

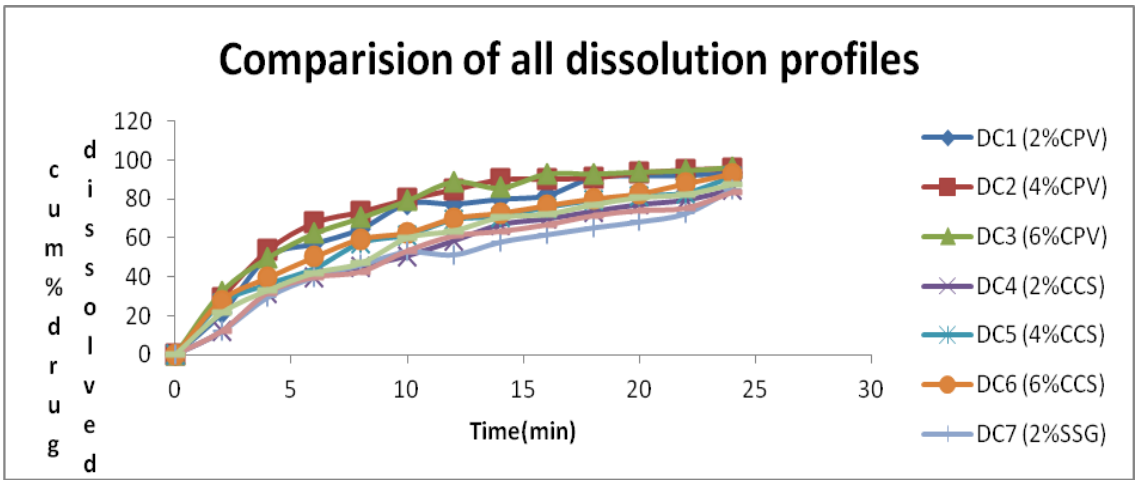

Fig no 6: Cumulative percentage drug dissolved vs time graph for MDTs by direct compression method.

Result of stability test

Table 13: Accelerated stability studies

Parameters	Time in months			
	0 (Initial)	1st month	2nd month	3rd month
Hardness (kg/cm^2)	2.7	2.7	2.6	2.6
Friability (%)	0.497	0.497	0.483	0.481
Disintegration time(sec)	89.16	89.16	88.72	88.72
Drug content (%)	93.47	93.25	93.18	92.87
In-vitro drug release (%)	96.56	96.44	96.36	96.20

Conclusion

By using three super disintegrants namely Crosspovidone, crosscarmellose sodium, sodium starch glycollate 9 formulations were prepared. In all the 9 formulations, formulation CD3 (crospovidone 6%) showed less disintegration time & good tabletting properties. When crospovidone was used as superdisintegrant it swells at faster rate upon contact with water and elimination of lump after disintegration when compared with sodium starch glycolate and crosscarmellose sodium. IR-spectroscopic studies indicated that there is no drug–excipients interaction. The stability study for the selected formulation CD3 was performed as per ICH guidelines. Stability study is carried out for 3 months at 40°C; 75%RH. The tablets were tested for release during the stability period and confirmed that results were found within the limits.

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