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RESEARCH ARTICLE

FORMULATION AND EVALUATION OF ORODISPERSIBLE LABETALOL TABLET FOR HYPERTENSIVE CRISIS

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ABSTRACT:

Labetalol HCl competitively blocks adrenergic stimulation of β-receptors within the myocardium (β_1-receptors) and within bronchial and vascular smooth muscle (β_2-receptors), and α1-receptors within vascular smooth muscle. Mouth dissolving drug delivery systems (MDTs) have acquired an important position in the market by overcoming previously encountered administration problems and contributing to extension of patent life. MDTs have the unique property of rapidly disintegrating and/or dissolving and releasing the drug as soon as they come in contact with saliva, thus obviating the requirement of water during administration. Taste masking was done by using Kyron-T 134 in ratio 1:3. The tablets were prepared by using direct compression method, using different Superdisintegrantsand they were then evaluated for pre and post compression parameters. More than 80% of drug was released from almost all the formulations within 5 min. Results of this study indicate among the superdisintegrants tried, Indion-414 showed the best result in 2% concentration.

Key words: Orodispersible Drug Delivery systems, Hypertensive crisis, Tablets.

INTRODUCTION:

Oral disintegrating/Orodispersible Drug Delivery systems:

Development of a formulation involves a great deal of study and experimental work to get Optimum results. While doing so we have to keep in mind various factors like choice of excipients, drug bioavailability, drug stability in required dosage form, cost effectiveness, manufacturing aspects i.e. scale-up and last but not the least we have to consider the patients compliance and convenience.

Fast disintegrating or orodispersible a tablet (ODTs) is one such novel approach to increase consumer acceptance by virtue of rapid disintegration, self administration without water or chewing. This novel type of delivery system offers convenience for treatment-resistant population who have difficulty in swallowing unit oral dosage form, namely tablets and capsules. These formulations are particularly beneficial to pediatric and geriatric patients, also during travelling where excess of water is not there. [1,2]

These fast disintegrating tablets can also be designed in such a way that the drug is absorbed through the buccal and esophageal mucosa as the saliva passes into the stomach. Due to this the bioavailability of the drug is greater than that observed for conventional dosage form.[3,4] Furthermore, the side effects caused by first pass metabolism may be reduced.[5]

Advantages[6-8]

- Improved patient compliance is the main advantage of this dosage form.
- Rapid onset of action as the tablet disintegrates within a matter of seconds.
- Useful for pediatric, geriatric and psychiatric patients.
- Suitable during traveling where water is may not be available.
- Give accurate dosing as compared to liquids.
- Ease of Administration to the patients who are unable or refuse to swallow solid unit dosage form.
- Achieve increased bioavailability/rapid absorption through pre-gastric absorption ofdrugs from mouth, pharynx & oesophagus as saliva passes down.
- The risk of chocking or suffocation during oral administration of conventional formulations due to physical obstruction is avoided, thus providing improved safety.

Challenges to develop ODT

- Rapid disintegration of tablet
- Avoid increase in tablet size
- Have sufficient mechanical strength
- Minimum or no residue in mouth
- Protection from moisture
- Good package design
- Compatible with taste masking technology

Disadvantages

- Tablets are very fragile and lack physical resistance; because the tablets are very porous and low compression forces are used to prepare them. they cannot be packed in conventional strips or in bottles and special packaging is required.
- Bitter drugs have to be taste masked by various techniques which in turn increases the time and cost of production.
- Drugs to be absorbed at a particular site cannot be given in this dosage form.

Ideal Characteristics of Orodispersible Tablets[9,10]

- ❖ Not require water for oral administration, yet dissolve / disperse/ disintegrate in mouth in matter of seconds.
- ❖ Have a pleasing mouth feel.
- ❖ Have an acceptable taste masking property.
- ❖ Be harder and less friable.
- ❖ Allow high drug loading
- ❖ Leave minimal or no residue in mouth after administration.
- ❖ Exhibit low sensitivity to environmental conditions (temperature and humidity).

Techniques for Preparing Orodispersible Tablets

US FDA considers fast disintegrating tablets as the new dosage form and hence new drug application is required for approval. Infact, at present ODTs are quick-dissolving dosage form recognized by FDA and listed in Approved drug products with therapeutic equivalence evaluation also called the orange book.

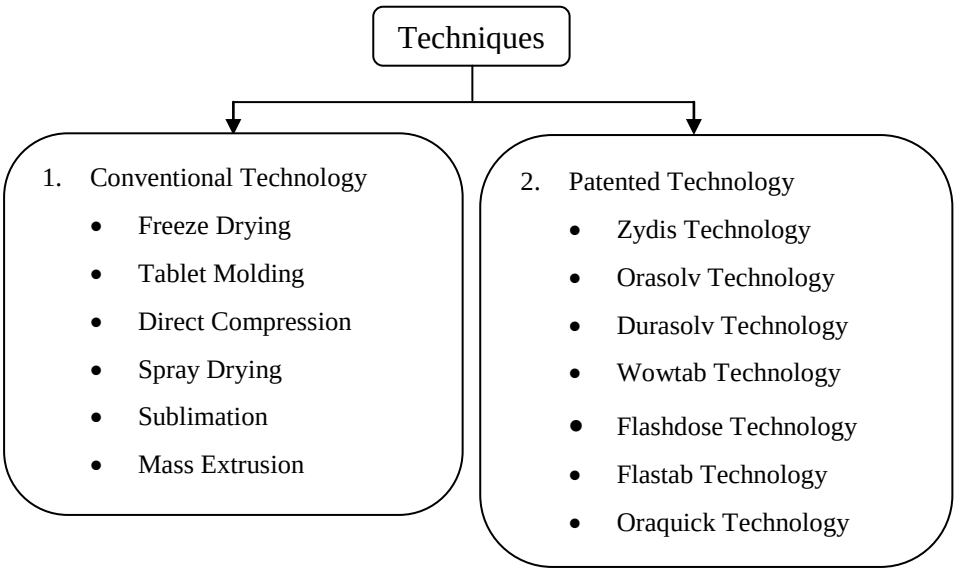

Fig. 1: Various technologies used in the preparation of fast disintegrating orodispersible tablets

Hypertensive crisis

Severely elevated blood pressure equal to or greater than a systolic 180mmHg or diastolic of 110mmHg sometime termed malignant or accelerated hypertension is referred to as a "hypertensive crisis", as blood pressures above these levels are known to confer a high risk of complications.

People with blood pressures in this range may have no symptoms.

A "hypertensive emergency", previously "malignant hypertension", is diagnosed when there is evidence of direct damage to one or more organs as a result of the severely elevated blood pressure. This may include

- ✓ Hypertensive encephalopathy, caused by brain swelling and dysfunction, characterized by headaches and an altered level of consciousness.
- ✓ Visual deterioration or breathlessness due to heart failure
- ✓ General feeling of malaise due to renal failure.

MATERIALS:

Labetalol Hcl (Dahlia pharmaceuticals pvt ltd, Ahemdabad), Kyron T-134 and Kyron T-154 (Corel pharma, Ahemdabad), Mannitol and Sodium starch glycolate (Rajesh chemicals), β-cyclodextrin (Research lab fine chem industries, Mumbai), Sorbitol and Sucrose (Kashyap sweetners, Mumbai), Indion-414 (Ion exchange india ltd, Mumbai), Cross povidone and Vanillin (Analab fine chemicals, Mumbai), Cross carmellose sodium (Seva fine chemicals, Ahemadabad), Aspartame (Balaji drugs).

METHOD:

Selection of taste masking material:

Preliminary study on various taste masking materials were carried out to select the taste masking agent like mannitol, sucrose, sorbitol, β-cyclodextrin, ion exchange resins such as Kyron –T 134, Kyron T-154 etc,

Procedure:

The drug and Kyron T-134 was taken in different ratios like 1:1, 1:2, 1:3, 1:4 etc. in this method the resin was properly weighed and taken in 40 ml of water and stirred for half an hour on magnetic stirrer so that resin swells. Then the Drug was added according to ratio and stirred for 45 hours continuously on magnetic stirrer. The solution was filtered and resinate was washed with water and dried. This complex was further used in ODT preparation

.

Table 1: list of taste masking agents used with its ratios

Category	Masking agents	Ratio of drug:masking agents
Sugars	Mannitol	1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7
	Sorbitol	1:1, 1:2, 1:3, 1:4, 1:5
	Sucrose	1:1, 1:2, 1:3, 1:4, 1:5
Polymeric materials	β-cyclodextrin	1:2, 1:3, 1:4, 1:5
Ion exchange resins	Indion 234	1:2
	Kyron T-134	1:1 1:2 1:3 1:4
	Kyron T-154	1:1 1:2 1:3 1:4

Procedure for preparation of Labetalol HCl ODT:

Labetalol HCl ODT was prepared by direct compression method. All the ingredients were weighed on analytical balance and mixed, the taste masked drug was weighed and added in the above mixture ensure proper mixing of all the ingredients. The tablets were compressed using 8mm punch curve shaped using geometric addition method.

Table 2: Formulae for ODT

Ingredients	F0	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Labetalol HCl	50	50	50	50	50	50	50	50	50	50	50	50	50
Kyron-T-134	150	150	150	150	150	150	150	150	150	150	150	150	150
Sodium starch glycolate	-	6	9	12	-	-	-	-	-	-	-	-	-
Cross carmellose sodium	-	-	-	-	3	6	9	-	-	-	-	-	-
Cross povidone	-	-	-	-	-	-	-	6	9	12	-	-	-
Indion-414	-	-	-	-	-	-	-	-	-	-	1.5	3	6
Aspartame	10	10	10	10	10	10	10	10	10	10	10	10	10
Mg stearate	6	6	6	6	6	6	6	6	6	6	6	6	6
Talc	6	6	6	6	6	6	6	6	6	6	6	6	6
Vanillin	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Mannitol	76.5	70.5	67.5	64.5	73.5	70.5	67.5	70.5	67.5	64.5	75	73.5	70.5
Total	300	300	300	300	300	300	300	300	300	300	300	300	300

Pre compression evaluation[11]:

Angle of Repose:

Angle of repose has been defined as the maximum angle possible between the surface of pile of powder and horizontal plane. The prepared granules were allowed to flow out of the funnel orifice fixed at a height of 2 cm from the surface on a plane paper kept on the horizontal platform. The gradual addition of the granules from the funnel mouth forms a pile of granules at the surface this is continued until the pile touches the stem tip of the funnel. A rough circle is drawn around the pile base and the radius of the granule cone was measured. Angle of repose was then calculated with the use of the following formula:

$$\tan\theta = h / r$$

Where, θ= angle of repose

h= height of the pile

r = average radius of the powder cone

Bulk Density:

Bulk density of the granules was determined by pouring gently 10g of sample through a glass funnel into a 50ml graduated cylinder. The volume occupied by the sample was recorded. The bulk density will be calculated as follows:

$$\text{Bulk Density (g/ml)} = \frac{\text{Weight of sample in grams}}{\text{Volume occupied by the sample}}$$

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Tapped Density:

10 grams of granule sample was be poured gently through a glass funnel into a 50ml graduated cylinder. The cylinder will be tapped from height of 2 inches until a constant volume will be obtained. Volume occupied by the sample after tapping will be recorded and tapped density will be calculated as follows:

$$\text{Tapped Density (grams/ml)} = \frac{\text{Weight of sample in grams}}{\text{Volume occupied by the sample}}$$

Carr's Index:

One of the important measures that can be obtained from bulk and tapped density determinations is the percent compressibility or the Carr's index, I, which is determined by the following equation**,**

$$I = \frac{\text{Tapped Density} - \text{Bulk Density}}{\text{Tapped Density}}$$

Hausner's ratio:

Hausner's ratio is defined as a ratio of a tapped density to bulk density. It is a measure of relative importance of interparticulate interactions. A Hausner ratio greater than 1.25 is considered to be an indication of poor flowability.

Method

Tapped density and bulk density were measured and the Hausner's ratio was calculated using the formula,

$$\text{Hausner's ratio} = \frac{\text{tapped density}}{\text{bulk density}}$$

Table 3: Evaluation of granules

Granules evaluation for flow properties					
Formulation	**Angle of repose (n=3)**	**Bulk density (n=3)**	**Tapped density (n=3)**	**Carr's index (n=3)**	**Hausner's ratio (n=3)**
F1	19.68 ± 0.22	0.648 ± 0.47	0.727 ± 0.91	10.92	1.12
F2	25.26 ± 0.25	0.582 ± 0.38	0.797 ± 0.67	27.02	1.37
F3	23.26 ± 0.29	0.638 ± 0.37	0.775 ± 0.96	17.67	1.21
F4	24.08 ± 0.26	0.618 ± 0.85	0.772 ± 0.67	20	1.25
F5	29.89 ± 0.18	0.638 ± 0.37	0.785 ± 0.83	18.20	1.22
F6	21.01 ± 0.2	0.619±0.22	0.725 ± 0.75	14.62	1.17
F7	27.33 ± 0.77	0.602 ± 0.31	0.762 ± 0.81	21.04	1.26
F8	26.44 ± 0.9	0.618 ± 0.85	0.772 ± 0.67	20	1.25
F9	25.29 ± 0.25	0.598 ± 0.42	0.747 ± 0.36	19.89	1.25
F10	21.42 ± 0.31	0.612 ± 0.25	0.765 ± 0.88	16.83	1.18
F11	24.08 ± 0.38	0.621 ± 0.54	0.775 ± 0.67	20	1.26
F12	26.31 ± 0.21	0.632 ± 0.82	0.787 ± 0.92	20	1.28

Post compression Evaluation:

Weight variation[12]:

It was performed as per the method given in the Indian pharmacopoeia. Tablets were randomly checked to ensure that uniform weight tablets were being made. Twenty tablets were selected randomly from each formulation, weighed individually and the average weight and % variation of weight was calculated.

Friability[12]:

20 tablets were weighed and placed in the roche friabilator test apparatus, the tablets were exposed to rolling and repeated shocks, resulting from free falls within the apparatus. After 100 evolutions the tablets were de-dusted and weighted again. The friability was determined as the percentage loss in weight of the tablets.

$$\%\text{friability} = 1 - \frac{\text{Weight of tablet after test}}{\text{Weight of tablet after test}} \times 100$$

Hardness:

Hardness was measured using the Monsanto hardness tester. Measure the pressure required to break diametrically placed matrix tablet, by a coiled spring.

Dimensions:

The thickness and diameter of the tablets was determined using a vernier caliper. Five tablets from each formulation were used and average values were calculated.

In-vitro Disintegration Studies[12]:

Tablets areplaced in the disintegration tubes and time required for complete disintegration, that is without leaving any residues on the screen is recorded as disintegration time. In about 6-8 ml of phosphate buffer 6.8 pH was taken in 10 ml of measuring cylinder .Tablet was placed in the cylinder and complete dispersion of tablet in the cylinder was recorded as the disintegration time.

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Table 4: Evaluation of tablets

Formulation	Weight variation (n=3)	Hardness (n=3)	Diameter (n=3)	Thickness (n=3)	Friability (n=3)
F1	299.8 ± 0.83	3.6 ± 0.28	8 ± 0.02	1.7 ± 0.01	0.24 ± 0.2
F2	300.1 ± 1.32	3.3 ± 0.57	8 ± 0.05	1.5 ± 0.02	0.83 ± 0.6
F3	300.4 ± 1.47	3.3 ± 0.57	8 ± 0.04	1.7 ± 0.03	0.22 ± 0.11
F4	301.0 ± 1.20	3.8 ± 0.28	8 ± 0.05	1.8 ± 0.04	0.31 ± 0.12
F5	299.8 ± 1.42	4.2 ± 0.28	8 ± 0.03	1.7 ± 0.02	0.72 ± 0.14
F6	300.3 ± 1.61	3.8 ± 0.28	8 ± 0.04	1.5 ± 0.01	0.64 ± 0.32
F7	301.3 ± 1.58	3.3 ± 0.57	8 ± 0.00	1.6 ± 0.02	0.55 ± 0.44
F8	300.3 ± 1.68	3.1 ± 0.66	8 ± 0.02	1.8 ± 0.05	0.33 ± 0.42
F9	300.1 ± 1.32	3.5 ± 0.56	8 ± 0.05	1.8 ± 0.03	0.62 ± 0.21
F10	302.4 ± 1.67	3.4 ± 0.19	8 ± 0.03	1.7 ± 0.04	0.53 ± 0.83
F11	300.6 ± 1.63	4.3 ± 0.76	8 ± 0.04	1.7 ± 0.05	0.41 ± 0.7
F12	300.7 ± 1.82	3.8 ± 0.59	8 ± 0.02	1.8 ± 0.06	0.82 ± 0.82

Wetting Time:

A piece of tissue paper folded twice was placed in a small Petri dish (ID =6.5 cm) containing 6 ml of simulated saliva pH 7.4, a tablet was put on the paper containing amaranth powder on the upper surface of the tablet, and the time required for formation of pink color was measured as wetting time.

Tablet Assay:

Ten tablets were accurately weighed and finely powdered. A quantity equivalent to 50 mg of Labetalol HCl was transferred to a 100 ml volumetric flask. To it, 50 ml of 0.1 N HCl was added and shaken for 1 hour to dissolve drug. The solution was filtered and residue was washed with 25 ml of 0.1 N HCl. The washing obtained was added to initial filtrate and volume was made upto 100 ml with 0.1 N HCl. From above solution 1 ml of stock solution was diluted to 10 ml. The drug content was determined spectrophotometrically at 301.5nm.

Table 5: In-vitro Disintegration time, Wetting time and Tablet assay

Formulation	Disintegration time (Sec.)	Wetting time (Sec.)	Tablet assay
F1	110	102	87.03
F2	89	75	93.02
F3	66	53	91.8
F4	80	69	94.58
F5	51	39	91.11
F6	45	32	96.17
F7	63	55	92.4
F8	55	43	98.18
F9	35	24	95.48
F10	45	35	96.16
F11	40	28	93.14
F12	25	17	99.71

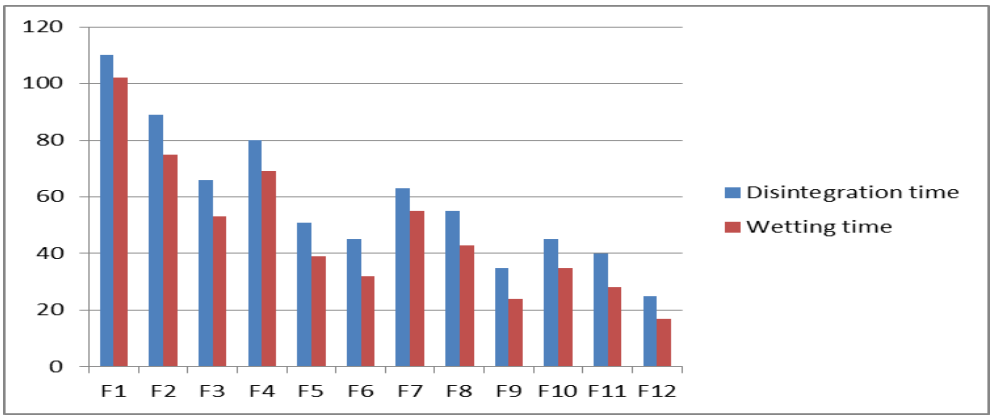

Fig. 2: Cumulative disintegration time and wetting time of Orodispersible tablet of formulations

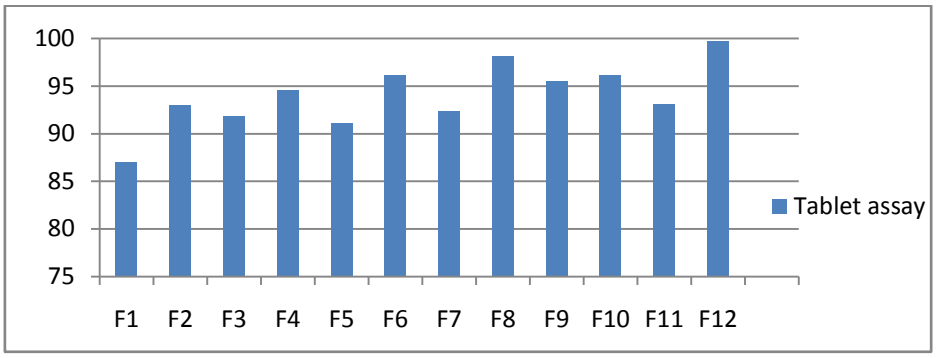

Fig. 3: Cumulative percentage drug content for Orodispersible tablet of formulations

Dissolution Studies:

Dissolution studies were carried out for all the formulation combinations in triplicate, employing USP XXIII paddle method (Apparatus 2) using 0.1N HCl, as the dissolution medium (500 ml) at 50 rpm and 37 ± 0.5ºC. An aliquot of sample was periodically withdrawn at suitable time intervals and volume replaced with equivalent amounts of fresh dissolution medium. The samples were analyzed spectrophotometrically at 301.5nm.

Dissolution study was carried out in pH 7.4 saliva media,using USP Apparatus type-2 (paddle),at 37ºC temperature.

Dissolution profile: - In-vitro dissolution profile of drug Labetalol HCl

Table 6: Dissolution profile of all formulations in pH-7.4 saliva media

Time in min	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
1	0.67	0.83	1.00	0.25	0.42	0.58	2.00	2.33	2.23	1.83	2.00	2.33
2	1.34	1.84	2.34	0.67	1.25	1.67	3.05	4.77	4.36	3.69	4.27	5.02
3	2.35	2.53	3.17	1.18	1.77	2.36	4.55	5.89	6.12	5.56	5.76	5.96
4	2.78	2.89	4.24	1.52	2.62	3.38	5.79	6.34	6.45	6.56	6.07	6.65
5	3.01	3.12	4.34	1.67	2.78	3.43	5.89	6.45	6.52	6.67	6.78	6.76

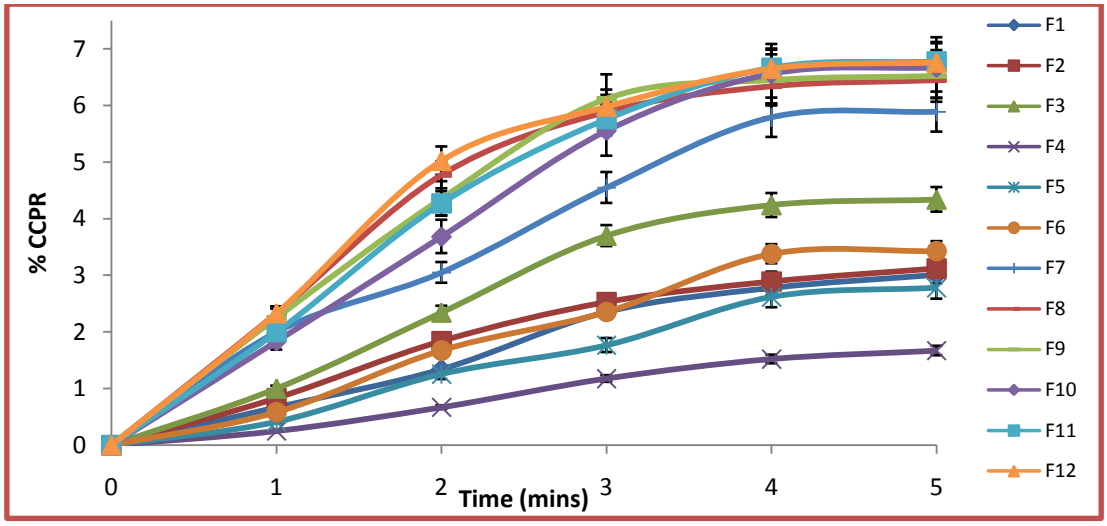

Fig. 4: Cumulative percentage drugs released from Orodispersible tablet formulations in saliva

Table 7: Dissolution profile of all formulations in 0.1 N HCl

Time in min	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
1	25.52	32.56	38.78	14.26	20.49	24.71	29.35	34.58	42.00	42.61	47.25	52.88
2	43.47	52.80	63.92	24.45	34.77	47.05	59.33	71.06	83.38	67.8	75.70	85.21
3	51.17	63.61	73.85	32.35	44.57	52.54	71.84	79.26	89.51	78.36	83.55	92.57
4	54.64	66.96	77.45	36.33	50.61	57.03	76.03	83.69	94.00	84.59	89.80	96.27
5	57.74	70.92	81.65	40.72	57.49	61.74	81.05	90.14	98.31	91.45	95.69	99.20

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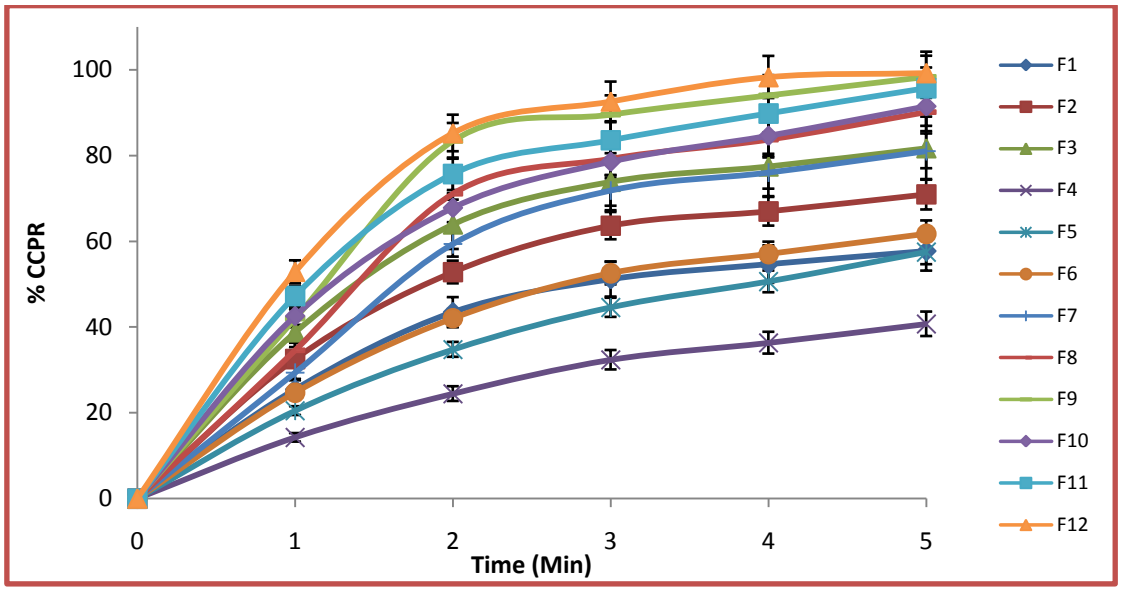

Fig. 5: Cumulative percentage drugs released from Orodispersible tablet formulations in 0.1 N HCl

RESULT AND DISCUSSION:

In the present work, ODTs of Labetalol HCl were prepared by direct compression technique using super disintegration such as Indion 414 to improve the bioavaibility of Labetalol HCl. The dispersion time of tablets were reduced by superdisintegrantsthat is Indion 414.

The flow property of polymer and drug was good. The taste of drug was bitter, so for masking the bitter taste of drug Kyron T-134 was used (drug and Kyron T -134 in ratio 1:3 respectively) by Ion exchange resins technique in which taste of drug was successfully masked.

Formulated tablets gives satisfactorily result for various physico-chemical evalution of tablet dimension, hardness, friability, weight variation, in-vitro dispersion time, wetting time and drug content.

The values of standard deviation for average weight and drug content of the tablet prepared indicate weight and drug content uniformity with in the batches prepared. Based on in-vitro disintegration time, formulation F12 found to be most promising and displayed a dispersion time of 25 sec.

The formulation F12 have displayed good water absorption capacity which indicates better and faster swelling ability of the disintegration in presence of little amount of water. It was observed from the results that Indion414 used formulation showed maximum dissolution rate of 99.18%.

From the present study, it may be concluded that the ODTs of Labetalol HCl can be prepared by direct compression method using new superdisintegrants Indion 414.

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