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# COMPARATIVE DISSOLUTION STUDIES OF PROPRANOLOL HCL BY USING DIFFERENT TECHNIQUES

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**Abstract:**

*Propranolol HCl is a beta blocker used for sudden anginal attacks and tremors due to fear etc. Rapid disintegration of the tablet is desired to achieve quick onset of action. For this, suitable disintegrants must be added and tablet must disintegrate within seconds. From this experiment it was found that CPV (an insoluble superdisintegrants) gives fastest disintegration attributed to its high swelling properties and the optimum concentration of CPV is 8%. Tablets were prepared by using three methods of which Effervescent method is evolved as best. The optimized formulation is subject to stability studies for 4 weeks by storing them at 40C/75%RH. Results of physical appearance, hardness, friability, disintegration test, and drug content have shown that there is no significant change at storage condition.*

**Keywords:** *Propranolol HCl, hardness, friability, disintegration test, and drug content.*

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## INTRODUCTION:

The oral route is the most favourable route for administration of drugs because of accurate dosage, low cost of therapy, self-medication, non-invasive method, and ease of administration leading to a high level of patient compliance [1]. MDTs are designed to disintegrate rapidly on contact with saliva and enable oral administration without water or chewing. MDTs are also called as orodispersible tablet (OT), mouth dissolving tablet (MDT), rapidly disintegrating tablet (RDT), fast dissolving tablet (FDT), fast melting tablet (FMT), melt in mouth tablet (MMT) and quick dissolve systems. US Food and Drug Administration Center for Drug Evaluation and Research (CDER) defines, in the 'Orange Book', an orodisperse tablet as "a solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue" [2]. European Pharmacopoeia described orodisperse tablets as 'uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed' and as tablets which should disintegrate within 3 minutes [3].

Suitable drug candidates for such systems include neuroleptics, cardiovascular agents, analgesics, antiallergics and drugs for erectile dysfunction. MDTs with good taste and flavour increase the acceptability of bitter drugs by various groups of population [4].

Propranolol HCl is a commonly used beta-blocker that is advocated for the treatment of hypertension. Apart from hypertension it is also used in the treatment of conditions such as angina pectoris, acute myocardial infarction, acute stress reactions, somatic anxiety and panic reactions. Propranolol HCl has a short half life, and is rapidly eliminated from the body due to hepatic metabolism. Thus by formulating it as MDT its degradation by liver can be bypassed and thus, its bioavailability can be increased. The rationale for developing a mouth dissolving dosage form was to provide for improved patience compliance, and management of hypertension, such that the bioavailability of drug may be increased over conventional oral tablets and to provide quick relief.

The objectives of current research were:

- To develop mouth dissolving tablets of Propranolol HCl using excipients like
- superdisintegrants.
- To conduct drug excipient compatibility study with the selected excipients.
- To evaluate precompression characteristics of powder mixture for flow properties
- like bulk density, angle of repose, cars index.
- To evaluate tablets for hardness, friability, disintegration time, wetting time, water
- absorption ratio etc.
- To carry out in vitro dissolution studies of tablet formulations.
- To conduct stability studies according to ICH guidelines.

## METHOD AND METHODOLOGY:

**Standard calibration curve:**

Preparation of Propranolol HCl standard graph in phosphate buffer pH 6.8.

Propranolol HCl 100mg was weighed and dissolved in a little of phosphate buffer pH 6.8 and volume was made up to 100ml in volumetric flask. From this stock solution I (100mg/ml), 1ml is withdrawn and diluted with phosphate buffer to 100ml giving stock solution II (1mg/ml or 1000 µg/ml). From this solution, 0.1ml, 0.2ml, 0.3ml, 0.4ml and 0.5ml are withdrawn and made up to 10ml with phosphate buffer to obtain many dilutions of 10µg/ml, 20µg/ml, 30µg/ml, 40µg/ml, 50µg/ml. Absorption of each solution was measured at 279nm using Shimadzu UV spectrophotometer using phosphate buffer as reference standard.

## METHODS OF PREPARATION OF MOUTH DISSOLVING TABLETS:

There are various conventional technologies developed for preparation of MDTs like freeze drying, spray drying, moulding, phase transition process, melt granulation, sublimation, mass extrusion and direct compression. Of the above methods, direct compression is the most economical and easiest method of tablet preparation. The following three techniques of preparation of MDTs have been adopted in this experiment:

- Disintegration method
- Effervescent method
- Sublimation method

**Preparation of Propranolol HCl mouth dissolving tablets by direct compression technique:**

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 (6%, 8%, 10% of tablet weight) and mannitol as

direct compressible vehicle. Tablets are compressed with 8mm diametric punches. The dose of drug taken is 40mg per 200mg tablet weight.

Composition of different batches of Propranolol HCl mouth dissolving tablets by direct compression method.

| Formulation ingredient | $DC_1$ | $DC_2$ | $DC_3$ | $DC_4$ | $DC_5$ | $DC_6$ | $DC_7$ | $DC_8$ | $DC_9$ |
|---|---|---|---|---|---|---|---|---|---|
| Propranolol HCl | 40mg | 40mg | 40mg | 40mg | 40mg | 40mg | 40mg | 40mg | 40mg |
| CPV | 12mg | 16mg | 20mg | - | - | - | - | - | - |
| CCS | - | - | - | 12mg | 16mg | 20mg | - | - | - |
| SSG | - | - | - | - | - | - | 12mg | 16mg | 20mg |
| Mannitol | 122mg | 118mg | 114mg | 122mg | 118mg | 114mg | 122mg | 118mg | 114mg |
| Aspartame | 10mg | 10mg | 10mg | 10mg | 10mg | 10mg | 10mg | 10mg | 10mg |
| SLS | 4mg | 4mg | 4mg | 4mg | 4mg | 4mg | 4mg | 4mg | 4mg |
| Talc | 6mg | 6mg | 6mg | 6mg | 6mg | 6mg | 6mg | 6mg | 6mg |
| Magnesium stearate | 6mg | 6mg | 6mg | 6mg | 6mg | 6mg | 6mg | 6mg | 6mg |
| Total | 200mg | 200mg | 200mg | 200mg | 200mg | 200mg | 200mg | 200mg | 200mg |

**Preparation of Propranolol HCl mouth dissolving tablets by effervescent technique:**

Mouth dissolving tablets of Propranolol HCl were prepared by effervescent method using citric acid and sodium bicarbonate as effervescent agents. Three superdisintegrants crospovidone, croscarmellose sodium and sodium starch glycolate along with anhydrous citric acid and sodium bicarbonate in different ratios (1:2; 1:1; 2:1) were used. All the ingredients are accurately weighed and triturated slightly and compressed using compression machine with 8 mm round punch by direct compression technique. A minimum of 50 tablets were prepared for each batch. The corresponding weights of all ingredients were taken as in Table 6.

Table 6: Composition of different batches of Propranolol HCl mouth dissolving tablets by effervescent method.

| Formulation ingredient | $EF_1$ | $EF_2$ | $EF_3$ | $EF_4$ | $EF_5$ | $EF_6$ | $EF_7$ | $EF_8$ | $EF_9$ |
|---|---|---|---|---|---|---|---|---|---|
| Propranolol HCl | 40mg | 40mg | 40mg | 40mg | 40mg | 40mg | 40mg | 40mg | 40mg |
| CPV | 16mg | 16mg | 16mg | - | - | - | - | - | - |
| CCS | - | - | - | 20mg | 20mg | 20mg | - | - | - |
| SSG | - | - | - | - | - | - | 20mg | 20mg | 20mg |
| Mannitol | 88mg | 98mg | 88mg | 84mg | 94mg | 94mg | 84mg | 94mg | 94mg |
| Aspartame | 10mg | 10mg | 10mg | 10mg | 10mg | 10mg | 10mg | 10mg | 10mg |
| Citric acid | 10mg | 10mg | 20mg | 10mg | 10mg | 20mg | 10mg | 10mg | 20mg |
| Sodium bi carbonate | 20mg | 10mg | 10mg | 20mg | 10mg | 10mg | 20mg | 10mg | 10mg |
| SLS | 4mg | 4mg | 4mg | 4mg | 4mg | 4mg | 4mg | 4mg | 4mg |
| Talc | 6mg | 6mg | 6mg | 6mg | 6mg | 6mg | 6mg | 6mg | 6mg |
| Magnesium stearate | 6mg | 6mg | 6mg | 6mg | 6mg | 6mg | 6mg | 6mg | 6mg |
| Total | 200mg | 200mg | 200mg | 200mg | 200mg | 200mg | 200mg | 200mg | 200mg |

**Preparation of Propranolol HCl mouth dissolving tablets by sublimation technique:**

Mouth dissolving tablets of Propranolol HCl were prepared by sublimation method using camphor as subliming agent. Two concentrations -10mg and 20mg camphor have been used. And two superdisintegrants crospovidone, croscarmellose sodium were used in 8% and 10% concentrations respectively as those concentrations are selected as best from the results of evaluation tests of tablets prepared by direct compression method. All the ingredients except camphor and lubricants are weighed and granules were prepared by wet granulation method. Then camphor and lubricants were added to the granules, mixed well and tablets were compressed. The compressed tablets were kept in vaccum oven for 1hr at 80°C. The tablets so obtained were subject to further tests.

**Table 7:** Composition of different batches of Propranolol Hcl mouth dissolving tablets by sublimation method.

| Formulation ingredient | $SB_1$ | $SB_2$ | $SB_3$ | $SB_4$ |
|---|---|---|---|---|
| Propranolol HCl | 40mg | 40mg | 40mg | 40mg |
| CPV | 16mg | 16mg | - | - |
| CCS | - | - | 20mg | 20mg |
| Camphor | 10mg | 20mg | 10mg | 20mg |
| Mannitol | 98mg | 88mg | 94mg | 84mg |
| Aspartame | 10mg | 10mg | 10mg | 10mg |
| Citric acid | 10mg | 10mg | 10mg | 10mg |
| SLS | 4mg | 4mg | 4mg | 4mg |
| Talc | 6mg | 6mg | 6mg | 6mg |
| Magnesium stearate | 6mg | 6mg | 6mg | 6mg |
| Total | 200mg | 200mg | 200mg | 200mg |

**EVALUATION OF MDTs:**

The following evaluation parameters of tablets need to be assessed.

**A. Evaluation of blends before compression:** The various characteristics of blends to be tested before compression are

***Angle of repose:*** Angle of repose is determined by using funnel method. The accurately weighed blend is taken in a funnel. The height of the funnel is adjusted in such a way that the tip of the funnel just touches the apex of the heap of blend. The drug-excipient blend is allowed to flow through the funnel freely on to the surface. The diameter of the powder cone is measured and angle of repose is calculated using the following equation. Angle of Repose less than 30 ° shows the free flowing of the material.

**Tan Θ = h/r**

Where, h and r are the height of cone and radius of the cone base respectively.

**Table 8:** Angle of repose as an indication of powder flow properties.

***Bulk density (BD):*** Apparent bulk density is determined by pouring a weighed quantity of blend into graduated cylinder and measuring the volume and weight. Bulk density can be calculated by using following formula:

**Bulk density = Weight of the powder / Volume of the packing.**

***Tapped density (TD):*** It is determined by placing a graduated cylinder, containing a known mass of drug-excipients blend. The cylinder is allowed to fall under its own weight onto a hard surface from the height of 10 cm at 2 second intervals. The tapping is continued until no further change in volume is noted. Tapped density can be calculated by using following formula:

**Tapped Density = (Weight of the powder / volume of the tapped packing)**

***Compressibility index:*** The Compressibility Index of the blends is determined by using bulk density and tapped density values. Compressibility Index can be calculated by using following formula:

**Compressibility Index (%) = [(TD-BD) X 100] / TD]**

***Hausner's ratio:*** A similar index to indicate the flow properties can be defined by Hausner's ratio. Hausner's ratio can be calculated by using following formula:

**Hausner's ratio = (Tapped density) / (Bulk density)**

Hausner's ratio <1.25 – Good flow

1.25 – Poor flow

**B. Evaluation of Tablets:** All the formulated MDTs were subjected to the following quality control tests

***Weight variation:*** The weight variation test is carried out in order to ensure uniformity in the weight of tablets in a batch. First the total weight of 20 tablets from each formulation is determined and the average

is calculated. The individual weight of the each tablet is also determined to find out the weight variation.

***Tablet Thickness:***Tablet thickness can be measured using a simple procedure. Five tablets are taken and their thickness is measured using Vernier callipers. The thickness is measured by placing tablet between two arms of the Vernier callipers.

***Hardness:*** The hardness of tablet is an indication of its strength. It is the force required to break a tablet by compression in the radial direction. The force is measured in kg and the hardness of about 3-5 kg/cm2 is considered to be satisfactory for uncoated tablets. Hardness of 10 tablets from each formulation is determined by Monsanto hardness tester, Pfizer hardness tester etc. Excessive hardness significantly reduces the disintegration time.

***Friability test:*** Friability is the loss of weight of tablet in the container due to removal of fine particles from the surface. Friability test is carried out to access the ability of the tablet to withstand abrasion in packaging, handling and transport. Roche friabilator is employed for finding the friability of the tablets. Weigh the 20 tablets from each batch and place in Roche friabilator that will rotate at 25 rpm for 4 minutes. All the tablets are dedusted and weighed again. The percentage of friability can be calculated using the formula

**% Friability = [(W1-W2)100]/W1**

Where, W1= Weight of tablet before test,

W2 = Weight of tablet after test

The pharmacopoeial limit of friability test for a tablet is not more than 1%. This test is not applicable for lyophilized and flashdose tablets, but is done for tablets prepared by direct compression and moulding. It is a difficult to achieve friability within this limit for MDT and to keep hardness to the lowest to achieve a minimum possible disintegration time.

***Disintegration test:*** The standard procedure of performing disintegration test for these dosage forms has several limitations and they do not suffice the measurement of very short disintegration times. The disintegration time for MDT needs to be modified as disintegration is required without water, thus the test should mimic disintegration in salivary contents. For this purpose, a petridish (10 cm diameter) was filled with 10 ml of water. The tablet was carefully put in the center of petridish and the time for the tablet to completely disintegrate into fine particles was noted.

***Wetting time:*** Wetting time is closely related to the inner structure of the tablets and to the hydrophilicity of the excipient. Wetting time corresponds to the time taken for the tablet to disintegrate when kept motionless on the tongue. A linear relationship exists between wetting time and disintegration time. Wetting time increases with an increase in compression force or a decrease in porosity. Five circular tissue papers of 10 cm diameter are placed in a petridish containing 6ml of blue dye solution. A tablet is carefully placed on the surface of the tissue paper. The time require for develop blue color on the upper surface of the tablet is noted as the wetting time.

***Water absorption ratio:*** A small piece of tissue paper folded twice is placed in a small petridish containing 6 ml of water. A tablet is put on the paper and the time required for complete wetting is measured. The wetted tablet is then reweighed and water absorption ratio is determine by using following formula

**Water absorption ratio = 100 (Wa−Wb) / Wb**

Where, Wb is the weight of tablet before water absorption

Wa is the weight of tablet after water absorption

***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. The percentage of drug released at various intervals is calculated using beer-lamberts law.

***Stability Studies:*** 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±1C/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.

## RESULTS AND DISCUSSIONS:

**Standard calibration graph of propranolol hcl:**

The results of standard curve preparation are observed as below

**Table 1:**Standard calibration graph of Propranolol HCl in phosphate buffer pH-6.8

| S.No | Concentration(µg/ml) | Absorbance at 279nm |
|---|---|---|
| 1. | 0 | 0 |
| 2. | 10 | 0.212 |
| 3. | 20 | 0.407 |
| 4. | 30 | 0.605 |
| 5. | 40 | 0.800 |
| 6. | 50 | 0.956 |

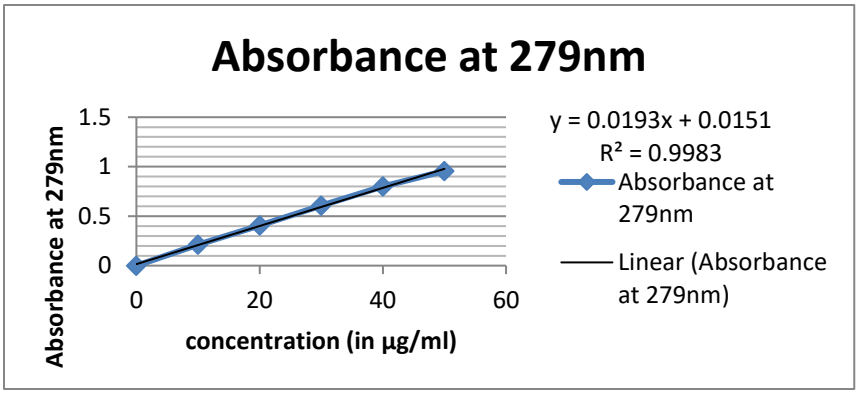



**Figure 1**: Standard calibration curve of Propranolol HCl

**Formulation of propranolol hcl tablets:**

**Formulation of Propranolol HCl mouth dissolving tablets by direct compression method:**

All tablet ingredients are weighed as per the compositions in table 5 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.

**Evaluation of powder blend:**

The prepared blend is evaluated for angle of repose, bulk density, tapped density, hausner's ratio, carr's index.

**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 |

**Evaluation of tablets:**
The tablets are subjected to the following quality control tests-weight variation, hardness, friability, disintegration test, wetting time, water absorption ratio and dissolution test:

**Table 3:**Evaluation of weight variation, hardness, thickness and friability of tablets prepared by direct compression method.

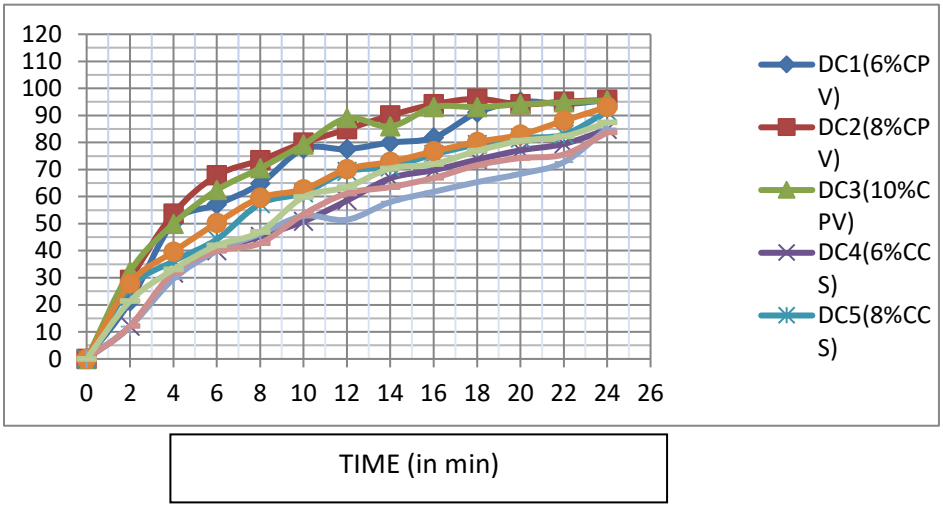
| Formulation code | Weight variation | Hardness (in kg/cm$^2$) | Thickness (in mm) | Friability (%) |
|---|---|---|---|---|
| $DC_1$ | 0.202±2.97% | 2.8±0.24 | 3.5 | 0.74% |
| $DC_2$ | 0.205±0.97% | 2.9±0.16 | 3.5 | 0.66% |
| $DC_3$ | 0.202±0.99% | 2.7±0.24 | 3.5 | 0.497% |
| $DC_4$ | 0.204±1.47% | 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 of tablets by direct compression method.

| 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 |
| $DC_2$ | 42.66±1.77 | 23.315±2.42 | 90.12±1.53 | 95.68 |
| $DC_3$ | 44.66±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 |

**Dissolution drug profile of MDT for preparations by direct compression method:**
In vitrodissolution studiesfor all the tablets was carried out by using USP Type II(paddle) dissolution apparatus at 50 rpm in 900 ml of phosphate buffer pH 6.8, maintained at 37±0.5ºC. 10ml samples were withdrawn at the 2min time intervals and absorbance checked using UV Spectrophotometer at 279nm. The cumulative percentage release of drug with respect to time is as follows:

**Figure 2:** Cumulative percentage drug released vs time graphfor MDTs by direct compression method.




**Formulation of Propranolol HCl mouth dissolving tablets by effervescent method:**
For MDTs prepared by effervescent method, superdisintegrantscrospovidone, croscarmellose sodium and sodium starch glycolate along with effervescent agents-anhydrous citric acid and sodium bicarbonate in different ratios (1:2;1:1;2:1)were used.All the ingredients were weighed, triturated slightly andcompressed using compression machine with 8 mm round punch. A minimum of 50 tablets were prepared for each batch.

**Evaluation Of Powder Blend:**
The prepared blend is evaluated for angle of repose, bulk density, tapped density, hausner's ratio, carr's index.

**Table 5:** Evaluation of powder blend of effervescent method.

| Formulation code | Angle of repose(θ) | Bulk density ($gm/cm^3$) | Tapped density($gm/cm^3$) | Hausner's ratio | Carr's index (%) |
|---|---|---|---|---|---|
| $EF_1$ | 30.68 | 0.540 | 0.633 | 1.17 | 14.69 |
| $EF_2$ | 29.18 | 0.543 | 0.652 | 1.2 | 16.71 |
| $EF_3$ | 29.72 | 0.531 | 0.611 | 1.15 | 15.06 |
| $EF_4$ | 29.32 | 0.572 | 0.670 | 1.17 | 14.62 |
| $EF_5$ | 27.71 | 0.552 | 0.689 | 1.248 | 19.88 |
| $EF_6$ | 27.32 | 0.546 | 0.678 | 1.24 | 19.46 |
| $EF_7$ | 26.45 | 0.543 | 0.689 | 1.26 | 21.11 |
| $EF_8$ | 29.64 | 0.580 | 0.677 | 1.16 | 14.32 |
| $EF_9$ | 27.29 | 0.569 | 0.703 | 1.23 | 19.06 |

**Evaluation Of Tablets:** ⟶
The tablets are subjected to the following quality control tests-weight variation, hardness, friability, disintegration test, wetting time, water absorption ratio and dissolution test:

Table 6: Evaluation of weight variation, hardness, thickness and friability of tablets prepared byeffervescent method.

| Formulation code | Weight variation | Hardness (in kg/cm$^2$) | Thickness (in mm) | Friability (%) |
|---|---|---|---|---|
| $EF_1$ | 0.206±1.60% | 2.6±0.16 | 3.5 | 0.25% |
| $EF_2$ | 0.202±1.68% | 2.7±0.24 | 3.5 | 0.496% |
| $EF_3$ | 0.206±0.97% | 2.7±0.24 | 3.5 | 0.415% |
| $EF_4$ | 0.206±0.58% | 2.7±0.24 | 3.5 | 0.413% |
| $EF_5$ | 0.208±1.25% | 2.85±0.24 | 3.5 | 0.331% |
| $EF_6$ | 0.202±1.13% | 2.9±0.16 | 3.5 | 0.332% |
| $EF_7$ | 0.204±0.78% | 2.6±0.16 | 3.5 | 0.496% |
| $EF_8$ | 0.202±0.79% | 2.7±0.24 | 3.5 | 0.498% |
| $EF_9$ | 0.204±0.58% | 2.8±0.24 | 3.5 | 0.660% |

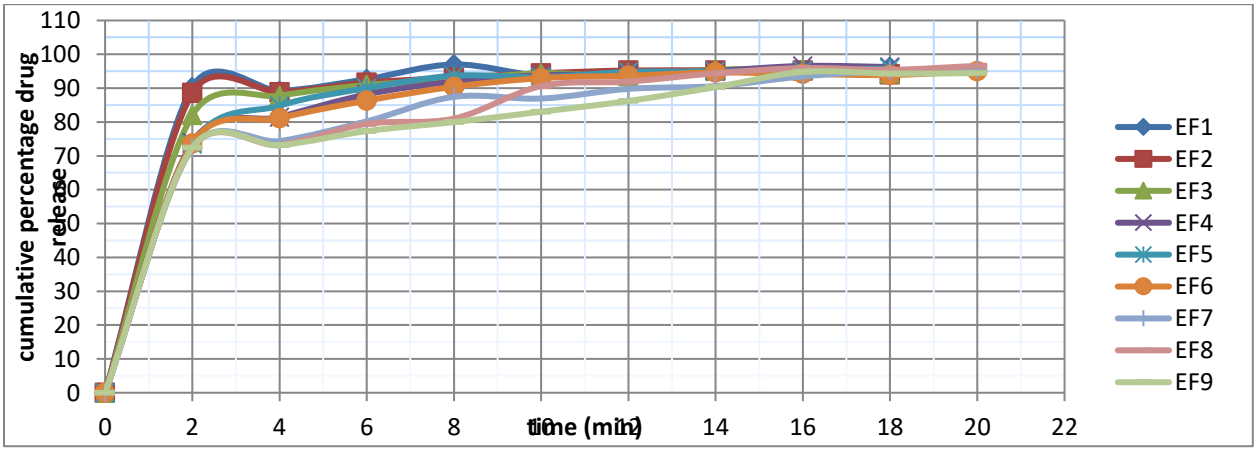
**Table 7:** Evaluation of wetting time, water absorption ratio, disintegration time and drug content of tablets by effervescent method.

| Formulation code | Wetting time (in sec) | Water absorption ratio(%) | Disintegration time(in sec) | Drug content (%) |
|---|---|---|---|---|
| $EF_1$ | 11±1.1 | 11.66±0.77 | 13.66±1.11 | 96.40 |
| $EF_2$ | 13.33±0.88 | 13.82±0.525 | 22±1.33 | 97.73 |
| $EF_3$ | 16.66±1.1 | 8.11±1.55 | 26.33±0.44 | 96.57 |
| $EF_4$ | 16±0.66 | 6.53±1.12 | 28±1.33 | 95.69 |
| $EF_5$ | 19±0.66 | 7.4±0.02 | 28±0.66 | 95.215 |
| $EF_6$ | 20.3±0.88 | 6.205±0.685 | 29.66±0.88 | 96.02 |
| $EF_7$ | 24.3±1.1 | 4.856±0.996 | 34.66±1.78 | 98.72 |
| $EF_8$ | 23±0.66 | 5.87±1.443 | 35.66±0.44 | 94.88 |
| $EF_9$ | 26.33±0.44 | 3.404±0.006 | 37±1.33 | 97.579 |

**Dissolution drug profile of MDT for preparations by effervescent method:**

In vitrodissolution studies for all the tablets was carried out by using USP Type II dissolution apparatus at 50 rpm in 900 ml of phosphate buffer pH 6.8, maintained at 37±0.5ºC. 10ml samples were withdrawn at the 2min time intervals and absorbance checked using UV Spectrophotometer at 279nm. The cumulative percentage release of drug with respect to time is as follows:

**Figure 3:** Cumulative percentage drug released vs time graph for MDTs by effervescent method.



**Formulation of Propranolol HCl mouth dissolving tablets by sublimation method:**
Mouth dissolving tablets of Propranolol HCl were prepared by sublimation method using camphor as subliming agent. Two concentrations-10mg and 20mg camphor have been used. And two superdisintegrantscrospovidone, croscarmellose sodium are used in 8% and 10% concentrations respectively as those concentrations are selected as best from the results of evaluation tests of tablets prepared by direct compression method. All the ingredients except camphor and lubricants are weighed and granules were prepared by wet granulation method. Then camphor is added to the granules, mixed well and tablets were compressed. The compressed tablets were kept in vaccum oven for 1hr at 80C. The tablets so obtained were subject to further tests.

**Evaluation of granules:**
The prepared blend is evaluated for angle of repose, bulk density, tapped density, hausner's ratio, carrs index.

**Table 8:** Evaluation of powder blend of sublimation method.

| Formulation code | Angle of repose(θ) | Bulk density ($gm/cm^3$) | Tapped density($gm/cm^3$) | Hausner's ratio | Carr's index (%) |
|---|---|---|---|---|---|
| $SB_1$ | 21.22 | 0.630 | 0.737 | 1.17 | 14.51 |
| $SB_2$ | 22.18 | 0.631 | 0.730 | 1.156 | 13.56 |
| $SB_3$ | 22.72 | 0.621 | 0.735 | 1.183 | 15.51 |
| $SB_4$ | 22.32 | 0.621 | 0.730 | 1.175 | 14.93 |

**Evaluation Of Tablets:**
The tablets are subjected to the following quality control tests-weight variation, hardness, friability, disintegration test, wetting time, water absorption ratio and dissolution test:

**Table 9:** Evaluation of weight variation, hardness, thickness and friability of tablets prepared by sublimation method.

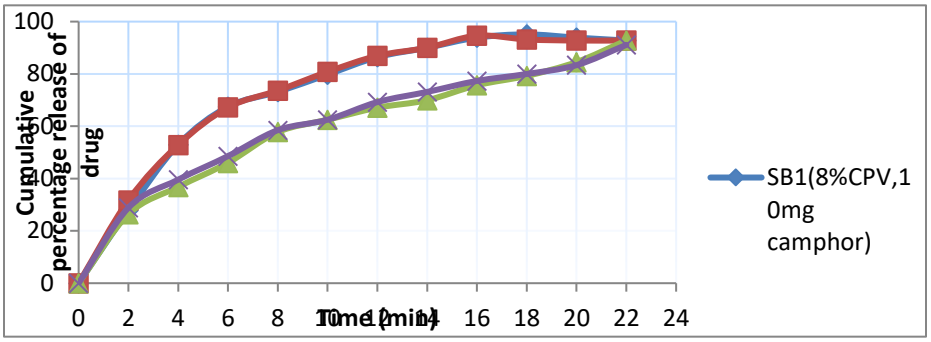
| Formulation code | Weight variation | Hardness (in $kg/cm^2$ ) | Thickness (in mm) | Friability (%) |
|---|---|---|---|---|
| $SB_1$ | 0.206±1.60% | 3.12±0.75 | 4 | 0% |
| $SB_2$ | 0.202±1.68% | 3±0.01 | 4 | 0.415% |
| $SB_3$ | 0.206±0.97% | 3±0.01 | 4 | 0% |
| $SB_4$ | 0.206±0.58% | 3.25±0.25 | 4 | 0.413% |

**Table 10:** Evaluation of wetting time, water absorption ratio, disintegration time and drug content of tablets by sublimation method.

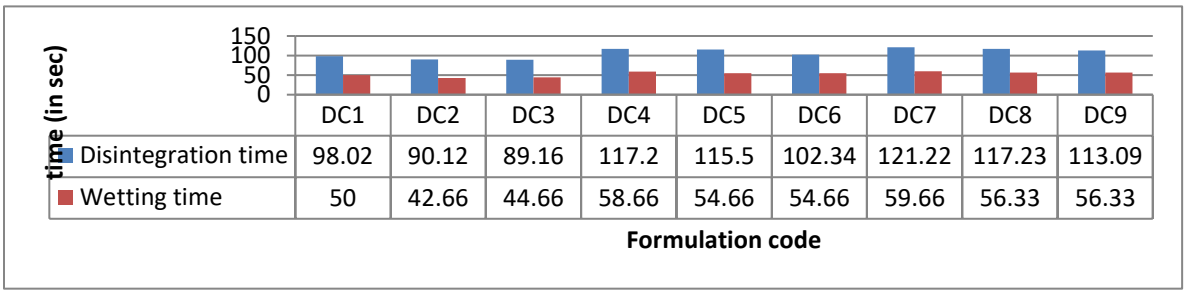
| Formulation code | Wetting time (in sec) | Water absorption ratio(%) | Disintegration time(in sec) | Drug content (%) |
|---|---|---|---|---|
| $SB_1$ | 26.3±0.44 | 4.15±1.24 | 59±1.33 | 91.022 |
| $SB_2$ | 24.3±1.1 | 8.32±1.18 | 58±2 | 94.09 |
| $SB_3$ | 38.66±2.44 | 3.57±0.733 | 65.33±0.44 | 93.068 |
| $SB_4$ | 39.33±1.77 | 4.04±0.24 | 65.33±1 | 93.068 |

**Dissolution drug profile of MDT for preparations by sublimation method:**
In vitro dissolution studies for all the tablets was carried out by using USP Type II (paddle) dissolution apparatus at 50 rpm in 900 ml of phosphate buffer pH 6.8, maintained at 37±0.5ºC. 10ml samples were withdrawn at the 2min time intervals and absorbance checked using UV Spectrophotometer at 279nm. The cumulative percentage release of drug with respect to time is as follows:

**Figure 4:**Cumulative percentage drug released vs time graph for MDTs by sublimation method.




**Comparision of disintegration time, wetting time and dissolution data of all tablet formulations:**
**Disintegration times of tablets by direct compression:**

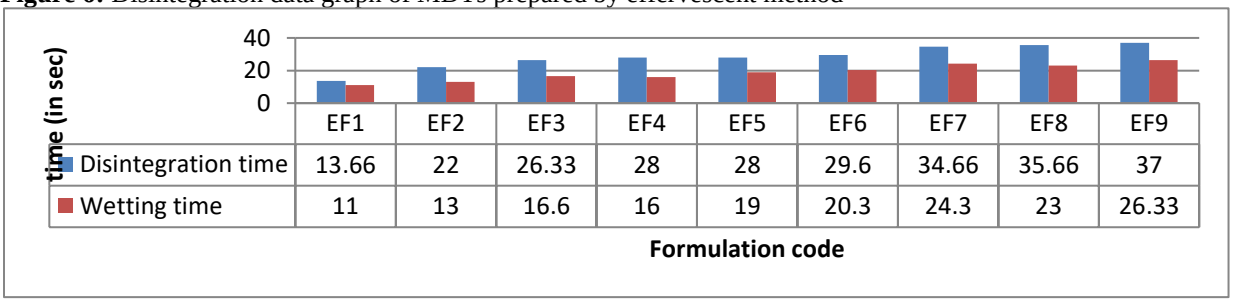



| | DC1 | DC2 | DC3 | DC4 | DC5 | DC6 | DC7 | DC8 | DC9 |
|---|---|---|---|---|---|---|---|---|---|
| Disintegration time | 98.02 | 90.12 | 89.16 | 117.2 | 115.5 | 102.34 | 121.22 | 117.23 | 113.09 |
| Wetting time | 50 | 42.66 | 44.66 | 58.66 | 54.66 | 54.66 | 59.66 | 56.33 | 56.33 |

**Figure 5:** Disintegration data graph of MDTs prepared by direct compression method

The disintegration times of tablets prepared by direct compression method show that formulation $DC_2$ gives fastest disintegration of within 90.1sec and lowest wetting time of 42.6 sec.

**Disintegration times of tablets by effervescent method:**
**Figure 6:** Disintegration data graph of MDTs prepared by effervescent method

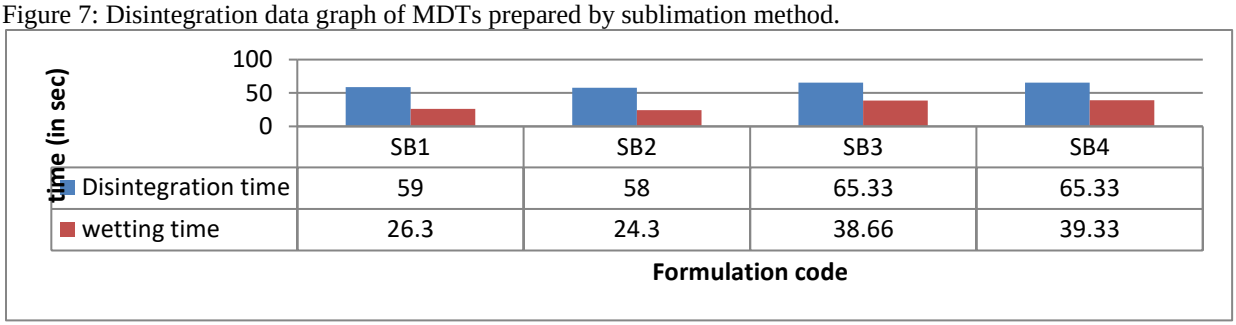



| | EF1 | EF2 | EF3 | EF4 | EF5 | EF6 | EF7 | EF8 | EF9 |
|---|---|---|---|---|---|---|---|---|---|
| Disintegration time | 13.66 | 22 | 26.33 | 28 | 28 | 29.6 | 34.66 | 35.66 | 37 |
| Wetting time | 11 | 13 | 16.6 | 16 | 19 | 20.3 | 24.3 | 23 | 26.33 |

The disintegration times of tablets prepared by effervescent method show that formulation $EF_1$ gives fastest disintegration of within 13.6sec and lowest wetting time of 11 sec.

**Disintegration times of tablets by sublimation method:**

Figure 7: Disintegration data graph of MDTs prepared by sublimation method.




The disintegration times of tablets prepared by sublimation method show that formulation $SB_2$ gives fastest disintegration of within 58sec and lowest wetting time of 24.3sec.Of all the batches, formulation EF1 shows lowest disintegration time and least wetting time.

**Dissolution profile comparison:**

T50%, T70%, T90% were calculated for all the formulations and compared.

**Table 11:** T50%, T70%, T90% of all tablet formulations.

| Formulation code | $T_{50\%}$(in min) | $T_{70\%}$(in min) | $T_{90\%}$(in min) |
|---|---|---|---|
| $DC_1$ | 4 | 9 | 18 |
| $DC_2$ | 3.8 | 7.4 | 14 |
| $DC_3$ | 4 | 8 | 15.2 |
| $DC_4$ | 10 | 16.2 | >24 |
| $DC_5$ | 6.4 | 11.6 | 23.5 |
| $DC_6$ | 6 | 15.4 | 22.5 |
| $DC_7$ | 9.8 | 21 | >24 |
| $DC_8$ | 9.6 | 17.6 | >24 |
| $DC_9$ | 8.8 | 14 | >24 |
| **$EF_1$** | **0.8** | **1.6** | **2** |
| $EF_2$ | 0.8 | 1.4 | 5.2 |
| $EF_3$ | 1 | 1.6 | 5.4 |
| $EF_4$ | 1.40 | 1.8 | 7.4 |
| $EF_5$ | 1.4 | 1.8 | 6 |
| $EF_6$ | 1.4 | 1.8 | 8 |
| $EF_7$ | 1.6 | 2 | 12 |
| $EF_8$ | 1.6 | 2 | 8 |
| $EF_9$ | 1.6 | 2 | 12 |
| $SB_1$ | 3.8 | 7.8 | 14 |
| $SB_2$ | 3.8 | 7.8 | 14 |
| $SB_3$ | 7.5 | 15.4 | 13.8 |
| $SB_4$ | 7.5 | 21 | 21 |

Among all the formulations, it is found that formulation $EF_1$ by effervescent method containing 8%w/w of CPV and citric acid, sodium bicarbonate in ratio (1:2) emerged as the best as t90%-time for 90% of drug to be released is 2 min based on the in vitro drug release characteristics. Thus, in this experiment of formulation of Propranolol HCl MDT, effervescent method is best suitable with formulation $EF_1$ containing 8%w/w of CPV and citric acid, sodium bicarbonate in ratio (1:2). It has emerged as the best with least disintegration time of 13.6sec and least wetting time of 11 sec and having a t90% =2 min (time taken for 90% drug release) drug release characteristics.

**Stability studies:**

The stability studies of optimized formula were carried out at 40 $^0$C and 75% RH using stability

chamber for six months. The different parameters that were studied are disintegration time, hardness, friability, drug content and dissolution rate. The optimized formulation was found to be stable in terms of physical appearance, drug content, disintegration time and *in vitro* drug release.

**Table 12:** Evaluation tests for best formulation.

| Stability Studies for best formulation $EF_1$ | Initial | After 4 weeks (stored at $40^0$C and 75% RH) |
|---|---|---|
| Colour | White | White |
| Weight Variation | 0.206±1.6% | 0.199±2% |
| Hardness | 2.6±0.16 | 2.5 |
| Friability (%w/w) | 0.25% | 0% |
| Disintegration time (sec) | 13.66sec | 10sec |
| %Cumulative drug release | 96.23% | 92.7% |

## DISCUSSION:

In present work an attempt was made to prepare Propranolol HCl mouth dissolving tablets which have advantage over conventional tablets in elders, paediatrics and patients with dysphagia.

The pre- and post-compression parameters of all formulations were evaluated. Effect of variables such as different class of superdisintegrants in varying concentrations on various pre and post parameters were evaluated using parameters like disintegration time, uniformity of weight, content uniformity, friability, hardness, thickness and stability studies.

**Identification:**

FTIR spectra itself shows the presence of all functional groups of the chemical drug. All the major spectral lines are similar to that of standard spectra in the drug monograph.

**Ftir compatibility study:**

Drug excipient studies are very crucial as they affect stability and potency of the formulation. FTIR techniques may be used to study interactions between drug and excipients used. After interpretation of FTIR spectra it can be concluded that as there is no major shifting, loss or appearance of functional peaks between spectra of drug and mixture of drug and excipients, the drug is compatible with excipients. Thus the excipients can be safely used in the formulations.

**Standard calibration curve:**

The lambda max for propranolol is 279nm. The standard calibration curve of Propranolol HCl was taken at 279nm It is obtained by plotting absorbance against concentration at 279nm and it was found to be was linear between 10 – 40 µg/ml range, $r^2$ was found to be 0.998 thus as it is linear graph, it obeys beer-lamberts law.

**Formulation of propranolol mdts:**

For formulation of MDTs the most easy and economic method is direct compression used. Still other methods technologies used are effervescence and sublimation. Tablets by all the three methods direct compression, effervescent method, and sublimation method were successfully prepared. Other excipients like mannitol, sweeteners, wetting agents, lubricants etc are added. The uniform blends of tablet were compressed at 8mm punch the hardness of tablets being maintained to below 3 $kg/cm^2$.

**Evaluation of powder blends:**

The powder blends for compression were evaluated for micromeretic properties (Tables 12, 16, 20). The bulk density and tapped density of powders are in the range of 0.509-0.572 and 0.599-0.703 respectively. These powders are free flowing in nature which is exhibited from its angle of repose of 28 to 31.9 and hausner's ratio of 1.15 to 1.3. Carr's index for all formulations was found to be below 23.69% indicating desirable flow properties.

**Evaluation of tablets:**

A total of nine batches by direct compression, nine by effervescent method and four formulations by sublimation method were prepared. Each prepared batch was subject to post formulation evaluation like weight variation, hardness, friability, disintegration time test, wetting time, water absorption ratio and invitro dissolution study.

**Weight Variation:**

All tablets satisfy the IP requirements for weight uniformity. In this study it was determined that weight of tablets varied in accordance with set limits. Hence weight variation test is passed.

**Hardness:** All the tablets showed good hardness of 2.5 to 3 $kg/cm^2$. The diluents mannitol imparts

crystalinity in the tablet which gives the hardness to tablets.

**Thickness:** These are non-pharmacopeial requirements but it will have an effect on packaging. Tablets prepared by direct compression and effervescent methods proved to be 3.5mm in thickness and those by sublimation 4mm thick.

**Friability:** A maximum loss of 1% is considered accepted for most formulations. All the formulations have passed this test.

**Disintegration time:** Tablets prepared using SSG showed slower disintegration than CCS which exhibited slower disintegration than tablets made by CPV. As co was increased, disintegration time and t50% decreased.

Tablets made by effervescent method showed very fast disintegration because of release of $CO^2$ on reaction with water. Also, evolution of $CO^2$ acts as taste masking agent. Different ratio of citric acid and sodium bi carbonate showed that ratio of 1:2 shows fastest disintegration of tablets in 13.6sec.

Tablets prepared by sublimation method show higher disintegration times than tablets prepared by direct compression. This is because of wet granulation method used in sublimation which subsequently increases hardness of tablets so increasing disintegration time.

**Wetting time:** It was found to be lowest for formulation $EF_1$ as 11sec.

**Drug content:** Preparations comply the test if content of each tablet is between 85% to 115%. The preparation fails to comply if more than one individual tablet is outside these limits. Since the quantity of drug is 40mg allowed range is 34mg to 46mg. All formulations proved to be in acceptable range.

**Dissolution data:** The dissolution behavior of all the formulations is presented in table. From dissolution data its concluded that formulation $EF_1$ by effervescent method containing 8%w/w of CPV and citric acid, sodium bicarbonate in ratio (1:2) emerged as the best as t90%-time for 90% of drug to be released= 2 min based on the invitro cumulative % drug release characteristics.

Thus, effervescent method is better than direct compression which is better than sublimation method in formulating Propranolol HCl MDTs.

## STABILITY STUDY:

The selected formulation was also subjected to stability studies by storing the tablets at 40C /75% RH in an incubator. Tablets were evaluated for parameters such as hardness, friability, disintegration time and drug content which indicated that there were not any major differences in results of different parameters. Thus, the selected formulation was stable.

Thus, in this experiment of formulation of Propranolol ODT, effervescent method is best suitable with formulation EF1 containing 8%w/w of CPV and citric acid, sodium bicarbonate in ratio (1:2) emerged as the best with least disintegration time of 13.6sec and least wetting time of 11 sec and having a t90% =2 min (time taken for 90% drug release) drug release characteristics.

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