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FORMULATION OF LYOPHILIZED ORAL DISINTEGRATING TABLETS OF PROPANOLOL

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ABSTRACT

Orally Disintegration Tablet (ODTs) are solid dosage forms containing active pharmaceutical ingredient (API) which disintegrate rapidly, usually less than 60 seconds without the need of water when placed on the tongue. Metoprolol, which is practically water insoluble, shows low bioavailability. weighed 100mg Propranolol was dissolved in 100ml of methanol solution to get a solution containing 100mcg/ml. Dilution: Aliquots of (0.1-1.0ml) standard solution were pipette out into 10ml volumetric flasks. The volume was made upto the mark with methanol solution to produce the concentration ranging from 1-10 mg/ml. The absorbance of each prepared solution was measured at 222nm in Shimadzu UV-1800 spectrophotometer against an appropriate blank (Methanol solution). Lyophilization is one of the techniques that can solve this problem in ODTs formulation. The resulting tablets were evaluated using parameters such as: hardness, friability, disintegration time in vitro, modified disintegration time, disintegration time in the oral cavity, wetting time, water absorption ratio, drug content determination, weight uniformity, and dissolution.

Keyword: ODTs (Oral disintegrating tablet), Lyophilized, Formulation, Propranolol, Disintegration, Gelatin

INTRODUCTION

Oral administration of drugs is preferred due to its ease of swallowing, distress avoidance, versatility and most significantly, patient compliance. The large number of patients find it difficult to swallow tablets and capsules, and do not take their medicines as prescribed. It is estimated that 50 % of the population affected by this problem, which finally results in a higher chance of noncompliance and ineffective therapy. For these reasons, tablets that can disintegrate in the oral cavity, have attracted enormous attention **[1]**. ODTs technology, which makes tablets dissolve or disintegrate in the oral cavity without any additional water intake, has drawn a great deal of attention. ODTs are a solid dosage form that provides the rapid disintegration or dissolution of solid to present as suspension or solution form even when placed in the mouth under limited bio-fluid **[2, 3]**. The excipients used in ODT technology areusually hydrophilic in nature and can be selected on the basis of drug's physicochemical properties like hydrophilicity or hydrophobicity **[18, 19]**.

The ODT formulation defined by the Food and Drug Administration (FDA) as "a solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds when placed upon the tongue". U.S. Food and Drug Administration approved Zydis, ODT formulation of Claritin (loratadine) in December 1996. It was followed by a Zydis ODT formulation of Klonopin (clonazepam) in December 1997, and a Zydis ODT formulation of Maxalt (rizatriptan) in June 1998. Further a number of drugs have been approved by regulatory authorities for ODT formulations **[4]**.

Advantages of ODTs

- The advantages of ODTs include **[12-17]**:
- No need of water to swallow the tablet.
- Compatible with taste masking and have a pleasing mouth feel.
- Can be easily administered to paediatric, elderly and mentally disabled patients.
- No residue in the oral cavity after administration.
- Manufacturing of the tablets can be done using conventional processing and packaging equipments at minimum cost.
- Allow high drug loading.
- Accurate dose can be given as compared to liquids.

- Dissolution and absorption of the drug is fast, offering a rapid onset of action.
- Advantageous over liquid medication in terms of administration as well as transportation.
- Some amount of drugs is absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach, thus reducing first pass metabolism, which
- offers improved bioavailability and thus reduced dose and side effects.
- No risk of suffocation due to physical obstruction when swallowed, thus offering improved safety.
- ODTs are suitable for sustained and controlled release actives.
- Unit packaging.

Drug :- Metoprolol Tartrate **[11]**

Drug Class: β1 receptor blocker

IUPAC name: (RS)-1-(Isopropyl amino)-3-[4-(2-methoxyethyl) phenoxy]propan-2-ol

Molecular formula: $C_{15}H_{25}NO_3$

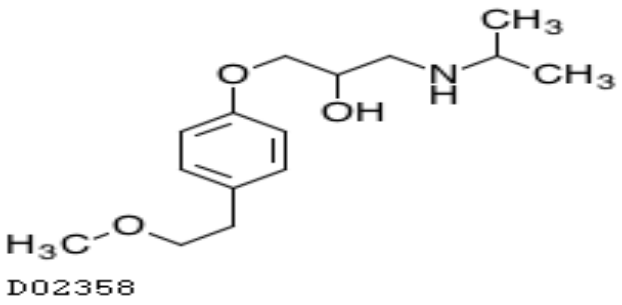


Figure 1: Propranolol structure

MATERIAL & METHODS:-

1 - Characterization of drug. Propranolol Hydrochloride

The drug sample obtained was identified by various analytical techniques such as IR Spectrosocopy, UV spectroscopy, melting point, partition coefficient and solubility etc. **[21, 23]**.

Organoleptic Property:-

Sr. No.	Properties	Inferences
1.	Colour	white or almost white powder
2.	Odour	Odourless
3.	Taste	Bitter

❖ **Meting point**

Melting point of Propranolol was determined by taking small amount of Propranolol separately in a capillary tube closed a one end and placed in a Thief's apparatus and the temperature at which Propranolol melt was recorded. This was performed in triplicate and average value was recorded.

Drug	Specification	Observation
Propranolol	110-115°C	109-112°C

❖ **Partition coefficient (P_{app})**

Partition coefficient is a measurement of drug's lipophilicity and its ability to cross cell membrane. Partition coefficient of Propranolol was determined at 37 ± 0.5 °C by taking 5 ml of octanol which was saturated with 5 ml of water by shaking with externally driven magnetic stirrer. After shaking the system remained undisturbed for half an hour. About 100 mg of drug was added to this solution and was shaken on wrist action mechanical stirrer. Two layers were separate through separating funnel and filterer through Whatman grade filter, and the amount of Propranolol solubilized, was determined by measuring the absorbance at 239 nm against reagent blank through double beam UV/Vis spectrophotometer (Shimadzu) in both the solution. Partition coefficient was determined as ratio of concentration of drug in octanol to the concentration of drug in water and the value were reported as log P.

$$(P_{app})\ K_{o/w} = \frac{\text{Concentration of drug in non aqueous phase}}{\text{Concentration of drug in aqueous phase}}$$

❖ **Solubility Studies**

Solubility studies was carried out with different solvents such as, 0.1 N HCl, phosphate buffer 6.8pH, water, ethanol, methanol in water bath shaker at 25°C and kept it for 24 hours.

FT-IR spectrum: Fourier transform infrared spectroscopy of different compounds was performed for identification of that particular compound. FT-IR Spectroscopy of pure drug, final optimized formulation was done using KBr pellets. Various peaks in FT-IR Spectrum were interpreted for identification of different group in the structure of pure drug and optimized formulaiton. FT-IR Spectroscopy can also be used to investigate and predict any physicochemical interactions between different components.

Drug Excipient Compatibility Study

Successful formulation of a stable and effective solid dosage form depends on the useful selection of excipients which are added to facilitate administration, promote

the consistent release and bioavailability of drug and protest it from degradation. FT-IR analysis of polymers and drug-polymer mixture were carried out in order to access drug polymen interaction. For this, the FT-IR of drug and polymers were carried out separately as well as in mixture of drug-polymer in the ratio 1:1

Establishment of calibration plot

❖ **Procedure for Standard Curve in methanol solution**

Standard Solution:. Accurately weighed 100mg Propranolol was dissolved in 100ml of methanol solution to get a solution containing 100mcg/ml.

Dilutions: Aliquots of (0.1-1.0ml) standard solution were pipette out into 10ml volumetric flasks. The volume was made upto the mark with methanol solution to produce the concentration ranging from 1-10 mg/ml. The absorbance of each prepared solution was measured at 222nm in Shimadzu UV-1800 spectrophotometer against an appropriate blank (Methanol solution). All the absorbance were conducted in triplicate (n=3).

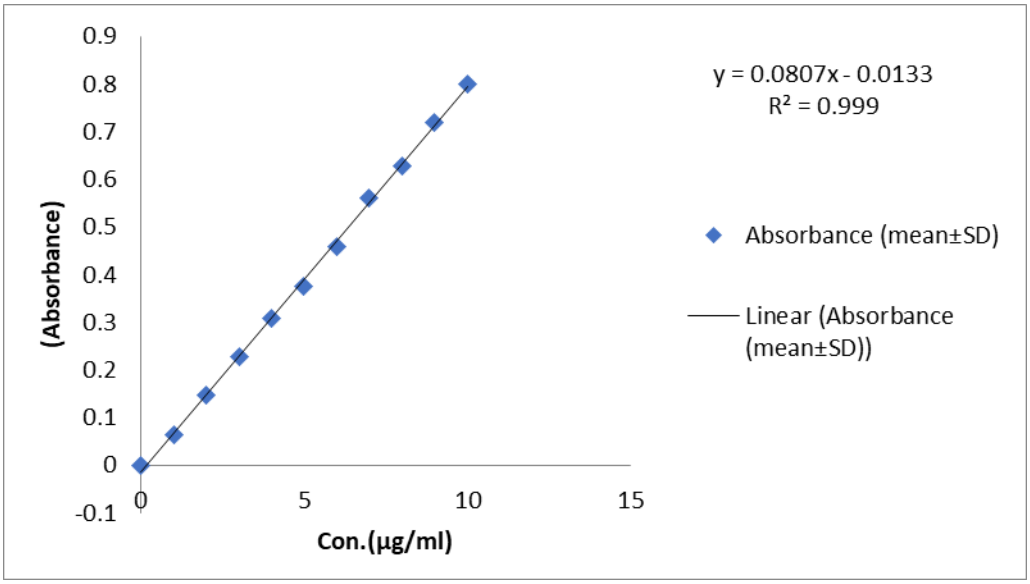


Figure 2: Standard Graph

RESULT & DISCUSSION:-

Preparation of Propranolol tartarate containing lyopihlized oral disingrating tablet [11-16]

The polymer at different concentrations were weighed and dissolved in 60 g of distilled water with gentle heat to aid faster dissolution at 60–65°C. A viscous polymeric solution was formed. Wheat starch and mannitol were added and dispersed in the polymeric solution. The final weight of the solution was adjusted to 100 g using distilled

water. The stirring was continued for 30 min. Each of 1 g of the base was casted into a tablet shaped plastic mould individually. The mould was stored in a freezer at -20°C for 4 h for the base to solidify. The mould was then transferred to a freeze dryer at -40°C for 12 h. The dried FDT was removed from the mould and stored in a desiccator.

Table 1: Composition of different drug loaded lyophilized oral disintegrating tablet-

Formulaiton code	Propranolol tartarate (mg)	Gelatin (%w/w)	HPMC E 15(%w/w)	Corn starch (%w/w)	Sucrose (%w/w)	Average weight of tablet (mg)
F1	30	1	-	2	20	250.65±0.55
F2	30	2	-	2	20	251.01±0.65
F3	30	3	-	2	20	250.44±0.38
F4	30	-	1	2	20	250.14±0.61
F5	30	-	2	2	20	251.69±0.41
F6	30	-	3	2	20	250.55±0.11
F7	30	-	2	1	20	251.01±0.28
F8	30	-	2	3	20	250.19±0.34
F9	30	-	2	2	10	250.97±0.17
F10	30	-	2	2	30	250.64±0.15

3 In vitro characterization of lyophilized oral disintegrating tablet

1-Weight variation of tablet

Twenty tablets were randomly taken from each batch and the weight of their average weight was determined. Then individual tablet was taken and its weight was calculated. That individual weight was compared with average weight. The weights were measured using weighing balance.

2- Hardness

The tablet hardness was evaluated using a TA. XT plus texture analyser (UK) equipped with a computer software Exponent Stable Micro Systems (Ver 5.1.1.0). A 2-mm flat surface probe was equipped on the texture analyser with a load of 100 g. The penetration force applied on the sample which penetrated a 2-mm depth into the sample was defined as the hardness of the tablet.

3- Thickness

The thickness of each FDT formulation was measured using a micrometre at the centre. Ten samples of each FDT formulation were measured **[15]**.

4- Friability test

Ten FDTs were used for the friability test using a friabilator. The FDTs were weighed and the initial total weight of ten tablets was determined by Analytical balance. After 100 rotations at 25 rpm, the FDTs were removed from the friability tester and again weighed **[14]**.

5- In-vitro disintegration time test

The disintegration time test determines whether tablets disintegrate within a prescribed time when placed in a liquid medium under experimental conditions. The in vitro disintegration time of the FDTs formulations was determined using a disintegration tester with 0.1N HcL at 37.0 ± 0.5°C. The disintegration time is defined as the time taken for FDT to completely dissolve and pass through the screen at the bottom of each tube of the disintegration tester, such that no solid residue remaining on the screen. A total of 6 FDTs were run for each formulation **[13]**.

6- Drug Content

The Drug Content was determined using the UV-Visible spectroscopy method. One FDT was dissolved in a 100 mL volumetric flask with methanol. The solution was subjected to sonication for 30 min. 1 mL of the stock solution was drawn out and was diluted with methanol to 10 mL in a volumetric flask and analysed using UV visible spectroscopy **[14]**.

7- In vitro drug release study:-

The dissolution studies were carried out on the optimum FDT formulation (30 mg Propranolol tartarate). Drug dissolution study was carried out in 900mL of 0.1M HCL (pH 1.0 ± 0.1) at 37.0 ± 0.5°C, using USP basket method at a stirring speed of100 rpm at preset time intervals of 5, 10, 15, 20, 30, 45, 60, 90 and 120 min, 1 mL of samples were withdrawn and immediately replaced with an equal volume of fresh dissolution medium. The samples were filtered through 0.45 lm membrane filter and the amount of drug released was determined using the uv-visible spectroscopy **[14]**.

Table 2: Evaluation of Tablets

Formulation code	Hardness	Thickness (mm)	% Friability	Disintigration time (Sec)std	Percentage drug content std
F1	0.885±0.017	5.47±0.025	0.084±0.002	101±0.58	81.45±0.003
F2	1.24±0.015	5.99±0.036	0.091±0.006	124±0.69	86.21±0.089
F3	1.68±0.029	6.41±0.094	0.099±0.004	168±0.42	89.63±0.097
F4	0.101±0.081	3.65±0.014	0.028±0.008	19±0.35	94.15±0.095
F5	0.587±0.035	3.88±0.058	0.031±0.001	25±0.71	96.05±0.048
F6	0.648±0.049	4.1±0.019	0.038±0.005	31±0.05	98.37±0.046
F7	0.367±0.051	3.61±0.021	0.027±0.009	19±0.69	96.24±0.025
F8	0.489±0.084	3.97±0.025	0.036±0.008	38±0.5	96.88±0.07
F9	0.602±0.038	3.81±0.027	0.035±0.004	27±0.02	97.14±0.088
F10	0.514±0.05	4.04±0.011	0.038±0.001	29±0.038	96.02±0.066

The average weight of all tablet was found to be in a range of 250.14±0.61to 251.69±0.41 **[17]**. The hardness of lyophilized ODT of all batches was found to be in a range of 0.101±0.081 to 1.68±0.029. demonstrated that the tablet thickness of all formulation was uniform and it was found to be in the range of 3.61±0.021–5.99±0.036mm.

.revealed that % friability of all formulation was found to be less than 1% indicating that tablet have sufficient mechanical strength showed no cracked, cleaved, or broken after tumbling.

Increasing in polymers concentration increased the disintegration time. The hardness of ODT increased due to higher level of cross-linking polymer network formed which reduced the porosity of the tablet. As a result, the disintegration time prolonged. Disintegration time of all formulation was uniform and it was found to be in the range of 19±0.69–168±0.42 sec.

percentage drug content of all formulation was found to be in a range of 81.45±0.003 to 98.37±0.046.

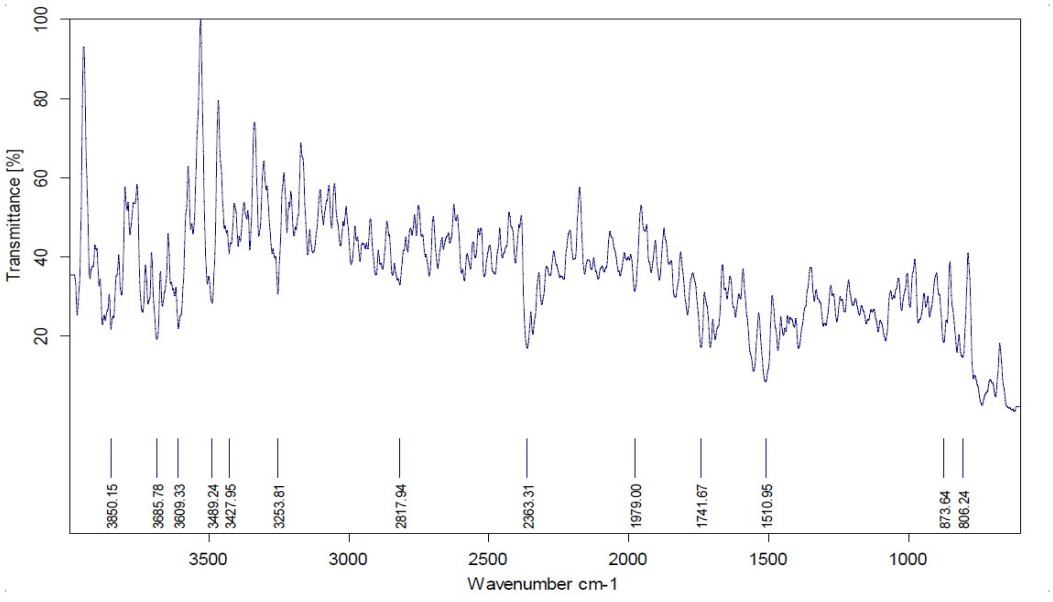
On the basis of above in vitro evaluation parameter formulation code F7 was selected for further evaluation.

The percentages of drug dissolved from FDTs F7 after 25 minutes were 98.21±1.23, indicate that the process used to prepare the FDTs greatly enhanced the extent and rate of dissolution of Propranolol from the prepared tablets **[17]**.

FT-IR spectral analysis

FT-IR analysis measures the selective absorption of light by the vibration modes of specific chemical bonds in the sample. The FT-IR spectrum of Propranolol is shown in **Figure 3**.

The main infrared peaks of the Propranolol are as follows: 3427.63 and 3253 cm^{-1}, attributable to its vibrational stretching of O-H and functional N-H bond, respectively. Other peaks are C = C aromatic stretching vibration at 1510 cm-; C-H streching at 2817 cm^{-1}. In formation theses peals were shifted and displayed with reduced intensity.



CONCLUSION:-

On the basis of above in vitro evaluation parameters & different test like friability ,hardness , thickness, percentage drug content, dissolution and disintegration time formulation code F7 was selected for further evaluation.as well as formulation code F7 is show more activity and FDT action compare to other formulation. Thus the prepared FDTs greatly enhanced the extent and rate of activity of Propranolol from the prepared tablets.

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