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# Preparation and Evaluation of Orodispersible Tablet Using Solid Dispersion of Isradipine

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## ABSTRACT

Isradipine is an antihypertensive agent that belongs to the biopharmaceutical classifications system (BCS) class 2, suffering from low bioavailability due to its low aqueous solubility. The present work aimed to prepare Oro dispersible tablets loaded with isradipine solid dispersion to achieve enhanced solubility and dissolution. Poloxamer 407 (PXM 407) in combination with the drug (PXM 407: isradipine) in (5:1) W/W% was used to prepare isradipine solid dispersion using solvent evaporation method. The product was evaluated for percentage of yield, drug content, and saturation solubility in phosphate buffer pH= 6.8. The produced solid dispersion mass was incorporated into orodispersible tablets (ODTs) by direct compression method utilizing different types and ratios of diluents (microcrystalline cellulose and mannitol) and superdisinegrants (croscarmellose and sodium starch glycolate). Five orodispersible tablet formulas were prepared; subsequently, they were evaluated for weight variation, content uniformity, hardness, friability, disintegration time, and dissolution testing. Formula number 2 (which composed of 30 mg of isradipine solid dispersion with microcrystalline cellulose and mannitol as diluents in addiction to 12% croscarmellose as super disintegrant) demonstrated the shortest disintegration time, and it had a better release as compared to pure isradipine -based orodispersible tablet.

**Keywords:** Isradipine, orodispersible tablet, Solid dispersion, microcrystalline cellulose.

## I. INTRODUCTION

Hypertension is a chronic health problem that results in blood pressure beyond the usual range of 120/80 mmHg. It is the key risk factor suggestive of several physiological problems.[1] Isradipine is a type of antihypertensive medication that belongs to the dihydropyridine (DHP) calcium channel blockers class. Its mechanism of action for managing hypertension (and, to some extent, angina) involves inhibiting calcium entry into the smooth muscle cells of the arteries. Isradipine is practically water-insoluble (<10 mg/L at 37 °C), but it is soluble in ethanol and freely in acetone and chloroform. It has a log p of 4.28 and an oral bioavailability of 15–24%.[3] Orodispersible tablets are an oral solid dosage form designed to improve the disintegration and dissolution characteristics of the drug, utilizing super-disintegrants as the primary ingredient[4]. Orodispersible tablets disintegrate in the oral cavity within a matter of seconds, which renders them highly effective for individuals suffering from dysphagia[5]. The pregastric absorption of drugs in the oral cavity as a result of the dispersion of the drug in saliva may increase the bioavailability of some drugs. In comparison to conventional tablets, the fraction of the drug that will suffer from first-pass metabolism is reduced[6]. Drug solubility is a crucial criterion for the development of orodispersible tablets. The solid dispersion (SD) approach is used to improve the solubility of poorly water-soluble drugs. This method involves dispersing the active pharmaceutical ingredient (API) in

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a carrier that physically modifies the API, making it more water-soluble[7]. The aim of this study is to formulate and evaluate orodispersible tablets of isradipine solid dispersion in poloxamer 407 using different types and ratios of superdisintegrants and diluents.

## II. METHODS AND MATERIAL

Isradipine was purchased from Hyperchem, China. PXM 407 was provided by Sigma alchrechi, Germany. Croscarmellose sodium (CCS), and sodium starchglycolate (SSG) were supplied by Pioneer pharmaceutical company. Mannitol and Microcrystalline cellulose.

**Preparation and evaluation of isradipine solid dispersion:**

Solvent evaporation method was used to prepare isradipine solid dispersion utilizing (PXM 407) as a hydrophilic carrier in a 5:1 (PXM 407: drug) weight ratio. Carrier was dissolved in ethanol with gentle stirring using a magnetic stirrer until a clear solution was obtained; then, the required amount of the drug was added with continuous stirring. The solution was poured into a Petri dish and, transferred to an oven, and dried at 40°C for 24 hours. Finally, the mass was grinded and sieved using No. 60 mesh sieve and stored protected from moisture for further investigations (7). The produced solid dispersion was evaluated for percentage of yield, drug content, and saturation solubility in phosphate buffer pH=6.8.

**Preparation of isradipine solid dispersion loaded orodispersible tablets:**

The orodispersible tablets containing isradipine solid dispersion equivalent to 5 mg of isradipine were prepared by direct compression method with various diluents and superdisintegrants, as shown in Table 1. Using mortar and pestle, the solid dispersion formula, diluents, superdisintegrant were mixed for 30 minutes. Subsequently, the lubricant and the glidant were added and mixed for 5 minutes. The resulting powder blend was then passed through sieve number 60 and then evaluated and incorporated into ODT.

**Pre-compression studies**

**Angle of repose**

The angle of repose of the resulting powder blend was determined by allowing the powder blend to flow through a funnel until the top of the conical mound that had been created just hit the funnel's tip. The height (H) of the cone was maintained at 2 cm, and after measuring the radius (r) of the resulting cone, we used the following equation to calculate the angle's tangent[8].

$$\tan\theta = H / r \qquad \text{Eq1}$$

Where theta is the angle of repose, H is the distance between the top of the cone and funnels lower tip, r is the radius of the resulted cone.

**Bulk density**

Bulk density represents the ratio of the powder mass to its bulk volume. The bulk density of the powder blend was measured by placing a specific weight of the powder in a clean and dry measuring cylinder, and the initial volume was recorded. The following formula used to calculate bulk density.[9]

**Bulk density = (Powder mass)/(Bulk volume) Eq 2**

**Tapped density**

The ratio of the powder mass to the tapped volume represents tapped density. The tapped density of the powder blend was measured by placing a specific weight of the powder in a clean and dry measuring cylinder and tapping the cylinder until the powder reached the minimum volume. The following equation is used to calculate taped density.[10]

**Tapped density = (Powder mass)/(Tapped volume) Eq3**

**Compressibility index (Carr's index)**

The flow properties of powder can also be determined by Carr's index, which is also an indication of the powder's compressibility. It can be calculated from the below formula.[11]

**Carr's index = (Tapped density-Bulk density)/(Tapped density)*100% Eq 4**

**Hausner's ratio**

Hausner's ratio is an indirect index of powder flow properties. The following equation is used to calculate Hausner's ratio.[12]

**Hausner's ratio = (Tapped density)/(Bulk density) Eq 5**

**Evaluation of isradipine ODTs**

**Weight variation**

Twenty tablets were individually weighed, and the average weight of all tablets was calculated. The USP requirements are met if no tablet differs by more than two times the percentage limits. Furthermore, no more than two tablets are outside the percentage limit of ±7.5%.[13]

TABLE I: COMPOSITION OF ODTS CONTAINING ISRADIPINE SOLID DISPERSION.

| Ingredient(mg) | Formula code | | | | |
|---|---|---|---|---|---|
| | T1 | T2 | T3 | T4 | T5 |
| Isradipine solid dispersion equivalent to 5mg | 30 | 30 | 30 | 30 | 30 |
| Microcrystalline cellulose | 57 | 55.5 | 57 | 55.5 | - |
| Mannitol | 133 | 129.5 | 133 | 129.5 | 185 |
| Sodium starch glycolate | - | - | 25 (10%) | 30 (12%) | - |
| Croscarmellose Sodium | 25 (10%) | 30 (12%) | - | - | 30 ( 12%) |
| Talc | 2.5(1%) | 2.5 (1%) | 2.5 (1%) | 2.5 (1%) | 2.5 (1%) |
| Mg Stearate | 2.5 (1%) | 2.5 (1%) | 2.5 (1%) | 2.5 (1%) | 2.5 (1%) |
| Total weight | 250 | 250 | 250 | 250 | 250 |

**Hardness test**

Three tablets were selected randomly from each batch to be tested for hardness using an Erweka electrical hardness tester. The device also records the tablet thickness and diameter. The hardness test is conducted to evaluate the tablet's ability to withstand different conditions, such as transportation, storage, and handling.[14]

**Friability**

In this test, twenty tablets were accurately weighed and placed into a plastic chamber of a Roche friability tester to test their ability to withstand transportation and attrition. The chamber rotates at 25 rpm for 4 minutes, dropping the tablets from a 6-inch height each time. After that, the tablets were removed, cleaned, and weighed again. The following equation is used to calculate friability percentage (13).

**Friability % = (initial weight -final weight / initial weight) * 100% Eq 6**

**Drug content**

Three tablets containing isradipine solid dispersion equivalent to 5 mg were selected randomly, and it was crushed in a dry, clean mortar. Subsequently, the powder was dissolved in 50 ml of ethanol in a volumetric flask, followed by sonication for 10 minutes. The resultant solution was filtrated using a 0.45-micron syringe filter and diluted appropriately to be assayed by a UV spectrophotometer at the drug-specific lamda max.[15]

**Disintegration time**

The disintegration test was performed on an Erweka disintegration device. Six tablets were selected, and a single tablet was placed in each tube. The basket is immersed in 900 ml phosphate buffer (pH = 6.8), and the temperature was maintained at 37 ± 2 ºC. The time required for the complete dissociation of tablets was recorded. For the tablets to be accepted, they should disintegrate within three minutes (15).

***In vitro* drug release study**

The dissolution study was performed for the optimum orodispersible tablet formula containing isradipine solid dispersion and for the orodispersible tablet containing pure isradipine. The *in-vitro* dissolution analysis of the orodispersible tablets was conducted in phosphate buffer (pH 6.8) using a Paddle apparatus (Erweka DT720 GmbH, Germany). A thermostatic water bath was used to maintain the temperature at 37±0.5°C. The device was set up to revolve at a rate of 75 revolutions per minute. A sample of 10 ml was collected from the dissolution medium at specific intervals. This evaluation was performed in triplicate.[15]

For the statistical analysis of the dissolution study for the ODTs containing isradipine solid dispersion and pure isradipine, the similarity factor ($f2$) was used for the statistical analysis of the dissolution profile, which is determined by the formula below:

$$f2 = 50.log\{100.[1 + \frac{1}{n}\sum_{t=1}^{n}(Rt - Tt)^2]^{-0.5}]\} \text{ . Eq 7}$$

The reference dissolution value (Rt), the test dissolution value (Tt), and the number of dissolution time points (n) are all represented at time t. When the $f2$ value is greater than 50 (within a range of 50 to 100), dissolution patterns are considered similar. On the other hand, dissimilar profiles are defined as those with a $f2$ value less than 50.[16]

**Comparison between the selected orodispersible tablet formula release profile and pure isradipine orodispersible tablet:**

The comparison between selected isradipine orodispersible tablets and orodispersible tablets containing pure isradipine regarding release profile was conducted in phosphate buffer (pH 6.8) and at 37.5 ºC±0.5.

## III. RESULTS AND DISCUSSION

**Evaluation of isradipine solid dispersion**

The drug content of the prepared formula was (99.5%±0.08) W/W%, which is within the acceptable range according to British pharmacopeia (15). Additionally, a high percentage of yield was obtained (93%). The saturation solubility of isradipine in phosphate buffer (pH=6.8) was significantly improved (p-value < 0.05) in the prepared isradipine solid dispersion (19.2±0.65 mcg/ml) in comparison to the parent drug solubility (1.2 mcg/ml). This may be attributed to the surfactant properties of the employed carrier.[17]

**Pre-compression evaluation of powder blends**

The results of angle of repose, carr's index, hausner ratio, and the type of flow for the prepared formulas are shown in Table 2. The pre-compression study of the powder blends indicated that all formulas except T5 (which was excluded from the study) exhibited acceptable flow ability and compressibility as indicated by angle of repose, Hausner' s ratio, and Carr's, respectively.

TABLE II: PRECOMPRESSION EVALUATION OF THE POWDER BLEND

| Formula Code | Hausner's ratio | Carr'sIndex | Compressibility | Angle of repose | Type of flow |
|---|---|---|---|---|---|
| T1 | 1.203±0.0706 | 17%±0.0479 | Fair | 37.217±0.30 | Fair |
| T2 | 1.21±0.11 | 17.5%±0.071 | Fair | 37.76±0.825 | Fair |
| T3 | 1.155±0.019 | 13%±0.015 | Good | 40±1.500 | Fair |
| T4 | 1.205±0.066 | 17%±0.046 | Fair | 39.42±0.335 | Fair |
| T5 | 1.441±0.257 | 30%±0.115 | Poor | 44.53±0.408 | Passable |

**Post-compression evaluation**

As shown in Table 3, T3 and T4 failed in the friability test so they were excluded from further investigations. This may be due to the rough surface of these two tablet formulations.[18,19] On the other hand T1 and T2 had weight variation and % friability within the acceptable range according to USP criteria (13). Besides, drug content and disintegration time agreed with British pharmacopeia (13,15). The results of the hardness test align with the accepted hardness range for orodispersible tablets 2-4 kg.[20] This provides the tablets with sufficient mechanical strength to withstand attrition during packaging, transporting, and handling, along with their ability to disintegrate rapidly in the oral cavity.

**Effect of diluent type on pre-compression parameters**

As shown in Table 3, the flowability and compressibility were largely affected by the type of diluent. The incorporation of microcrystalline cellulose into the powder blend of T1, T2, T3, and T4 resulted in a reduction in the angle of repose and better compressibility when compared with T5, in which only mannitol was used. This is possibly due to the reduction of interparticle friction and cohesion by microcrystalline cellulose.[21] The latter formula had a higher angle of repose and poor compressibility; this may be attributed to the needle-like shape of the mannitol particle.[22]

TABLE III: POSTCOMPRESSION EVALUATION OF ODTS.

| Formula code | Drug content mg | Hardness (Kg) | Friability | Weight | Disintegration time |
|---|---|---|---|---|---|
| T1 | 104.4%±0.040 | 3.94±0.15 | 0.80% | 248.835 | 2.48 |
| T2 | 95%±0.356 | 3.36±0 | 0.95% | 249.278 | 2.17 |
| T3 | - | 3.401±0.47 | Failed | 249.82 | - |
| T4 | - | 3.095±0.58 | Failed | 249.03 | - |

**Effect of superdisintegrant on post-compression parameters**

Both T1 and T2 show rapid disintegration, as shown in Table 3. This can be attributed to the presence of a superdisintegrant (Croscarmellose), which has both swelling capacity and water-wicking ability.[23] The disintegration time of T2 was faster as compared to T1. This is because the disintegrating effect of superdisintegrants is often concentration-dependent.[24]

**Selection of optimum ODT formula**

T2 was selected as the optimum ODT formulation as it has a good flow property, general appearance, friability, and the shortest disintegration time.

***In-vitro* dissolution of the ODT**

Figure 1 shows the dissolution behavior of T2 as compared to an ODT containing pure isradipine as a reference in phosphate buffer pH=6.8. The ODT containing isradipine solid dispersion (T2) demonstrated

complete dissolution after 30 minutes, while only 70% of the drug was released from the ODT incorporating pure isradipine. Additionally, *f2* similarity factor is approximately 31.96 (below 50), indicating that dissolution profiles are dissimilar.

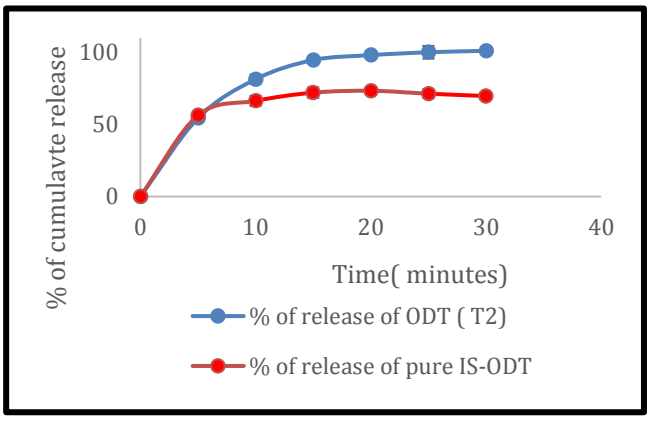


Fig 1: The dissolution profile of ODT(T2) as compared to pure isradipine ODT, N=3.

## IV. CONCLUSION

Isradipine prepared as solid dispersion utilizing PXM 407 as a carrier was an efficient method to enhance its solubility. Additionally, ODTs containing isradipine solid dispersion were prepared successfully after optimizing the type and the ratio of the diluents and superdisinitegrants. The ODT formulation contains croscarmellose (12%) as a super disintegrant and microcrystalline cellulose: mannitol demonstrated good flow properties, shortest disintegration time.

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