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ENHANCEMENT OF SOLUBILITY AND DEVELOPMENT OF ORODISPERSIBLE TABLETS OF ANTIHYPERTENSIVE DRUG

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ABSTRACT

This study aimed to enhance the solubility and develop orodispersible tablets of an antihypertensive drug Irbesartan, addressing the challenge of poor solubility often encountered with such medications. Solid dispersion formulations were prepared using different ratios of the drug and PEG 4000, a polymer known for its solubilizing properties. Evaluation of solubility enhancement revealed that the 1:3 ratio of drug to PEG 4000 exhibited the highest percentage enhancement, indicating the effectiveness of solid dispersion formulations. Subsequently, optimized orodispersible tablets were developed based on evaluations of compressibility, disintegration time, and dissolution behavior. Formulation F7 emerged as the optimized formulation, demonstrating the shortest disintegration time and rapid drug release. *In vitro* dissolution testing showed that increasing the concentration of disintegrant led to higher drug release rates, with solid dispersion technology significantly enhancing the dissolution rate and efficiency of the antihypertensive drug. Overall, the developed orodispersible tablets hold promise for improving the oral delivery of the antihypertensive drug, offering rapid disintegration and efficient drug release kinetics. This research contributes to addressing the solubility challenges associated with antihypertensive medications, potentially enhancing patient compliance and therapeutic outcomes.

Keywords: Solubility Enhancement, Irbesartan, Orodispersible tablets, formulation, Characterization.

INTRODUCTION

Irbesartan, an angiotensin II receptor antagonist, is a widely used antihypertensive medication known for its efficacy in the management of hypertension and related cardiovascular conditions. Despite its therapeutic benefits, Irbesartan is characterized by poor aqueous solubility, which can lead to challenges in achieving desired therapeutic concentrations and onset of action. The formulation of Irbesartan into oral dosage forms with enhanced solubility and rapid onset of action is therefore of significant interest in pharmaceutical research (Arora *et al.,* 2005). In recent years, various strategies have been explored to enhance the solubility of poorly soluble drugs like Irbesartan, including solid dispersion, cyclodextrin complexation, and nano-suspension formulations. These approaches aim to increase the dissolution rate and bioavailability of the drug, thereby improving its therapeutic efficacy (Zhang *et al.,* 2002).

Solid dispersion techniques, such as solvent evaporation, co-precipitation, and spray drying, have been widely investigated for enhancing the solubility of Irbesartan.

By dispersing the drug within a hydrophilic carrier matrix, solid dispersion formulations can improve drug wettability and dissolution, ultimately leading to enhanced bioavailability (Kim *et al.,* 2010). Furthermore, the development of orally disintegrating tablets (ODTs) offers a promising approach to improve patient compliance and convenience, particularly for elderly or dysphagic patients who may have difficulty swallowing conventional tablets. ODTs disintegrate rapidly in the oral cavity upon contact with saliva, facilitating easy administration without the need for water. This introduction aims to explore the recent advancements in the enhancement of Irbesartan solubility and the development of orally disintegrating tablets for improved patient convenience and compliance. By reviewing the relevant literature and discussing key findings from previous studies, this research seeks to contribute to the growing body of knowledge on novel drug delivery systems for antihypertensive medications.

MATERIALS AND METHODS

Optimization of drug: polymer ratio

All the ingredients were weighed accurately and passed through sieve no. 85 in order to obtain powder of fine particle size with narrow size distribution. The physical mixtures of drug with carrier PEG 4000 was prepared indifferent concentration by slightly grinding the drug and carrier in mortar for 2 min. The drug: PEG 4000 ratio which was taken as 1:1, 1:2, and 1:3 respectively. Then the resultant powder was passed through sieve no 85 and was stored in desiccator for 2-6 hrs to carry out further analysis. The prepared physical mixture was subjected to spectrophotometric method.

Preparation of solid dispersion of Irbesartan

For the preparation of Irbesartan-PEG 4000 solid dispersion by conventional method, PEG 4000 was weighed and a measured amount of Irbesartan was added and stirred, sample was pulverized with use of a pestle and mortar and sieved through a 400-mm mesh. 10mg of Irbesartan PEG 4000 powder (containing 75mg of Irbesartan and 275mg of PEG 4000) and was used for further investigations (Meka *et al.,* 2012).

Evaluation of dispersion dispersion

Percentage drug content

For the determination of Irbesartan content, dispersion equivalent to 10 mg of Irbesartan, were weighed and extracted with 10 ml of methanol by mechanical mixing for 5min followed by centrifugation at 10,000 rpm for 5 min on a centrifuge. The supernatant was filtered through 0.45µ membrane filter, and the filtered solutions were suitably diluted and analyzed for Irbesartan at 230nm using a validated UV spectrophotometric method.

Formulation development of orodispersible tablets of Irbesartan

The orodispersible tablets of Irbesartan were prepared using the sodium starch glycolate, Crospovidone and croscarmellose sodium as superdisintegrant, mannitol as diluent, aspartame as sweetening agent, and talc as

flow promoter and magnesium stearate as lubricant, the composition of each batch is shown in Table no. 1. The raw materials were passed through a 100-mesh screen prior to mixing. The drug and other ingredients were mixed together and a sufficient quantity of alcoholic solution of PVP K-30 (10%w/v) was added and mixed to form a coherent mass (Suryadevara *et al.,* 2016). The wet mass was granulated using sieve no. 12 and regranulated after drying through sieve no. 16. Granules of the all formulations were then dried in a vacuum oven (Vertex, VT4810) at 60°C for 12 h resulting in localized drying. The final moisture content of the granules was found to be between 1- 2%, which was determined using an IR moisture balance. During drying, the menthol sublimed with the formation of a porous structure on the surface of the tablet. The dried granules were then blended with talc, magnesium stearate and compressed into tablets using flat face round machine on a Rimek-I rotary tablet machine.

Evaluation of Precompression Parameter

Bulk density: Both loose bulk density (LBD) and tapped bulk density (TBD) were determined (Martin, 2001). Accurately weighed amount of granules taken in a 50 ml capacity measuring cylinder was tapped for 100 times on a plane hard wooden surface and estimated the LBD and TBD, calculated by using following formulas.

Compressibility index: Percent compressibility of powder mix was determined by carr's compressibility index, calculated by using following formula (Aulton and Wells, 1988).

Hausners ratio: It is determined by comparing tapped density to the bulk density by using following equation:-

Housner's ratio = Tapped bulk density/loose Bulk density

Evaluation of post compression parameter

Shape and colour of tablets

Uncoated tablets were examined under a lens for the shape of the tablet and colour was observed by keeping the tablets in light.

Thickness test

Three tablets were picked from each formulation randomly and thickness was measured individually. It is expressed in mm and standard deviation was also calculated. The tablet thickness was measured using dial-caliper (Mitutoyo, Japan) (Lachman and Lieberman, 1990).

Weight variation test

Twenty tablets were selected randomly from each formulation and average weight was determined. The tablets were weighed individually and compared with average weight. The U.S Pharmacopoeia allows a little variation in the weight of a tablet. The following percentage deviation in weight variation is allowed (Carr *et al.,* 1965).

Hardness test

The hardness of tablet was measured by Pfizer hardness tester and results were expressed in Kg/cm^2 (Willard *et al.,* 2007).

Friability test

For this, 20 tablets were taken from each formulation and the friability was determined using Roche friabilator. The equipment was run for 4min at 25 revolutions per minute. The

tablets were taken out, dedusted and reweighted and % friability was calculated. The friability was determined as the mass loss in percent according to Equation:-

$$\%\text{Friability} = (\text{Loss in weight}/\text{Initial weight}) \times 100$$

The test complies if tablets not loss more than 1% of their weight.

Uniformity of drug content

The test is mandatory for tablets with 10 mg or less weight of active ingredient. Ten randomly selected tablets from each formulation (F1 to F9) were finely powdered and Drug equivalent to 10 mg of drug dissolved in 10 ml phosphate buffer (pH 6.8) sonicate it for 20 minutes, till the entire drug leached out from complex, then the solution was filtered through whatman filter paper No. 41. From this Solution take 1 ml and Diluted up to 100 ml with phosphate buffer (pH 6.8) and the drug content was determined spectrophotometrically at 230 nm (Swamy *et al.,* 2021).

Dissolution rate studies

The prepared tablets were evaluated for *in vitro* drug release. The drug release studies were carried out using USP XXII paddle type Dissolution test apparatus. The dissolution study was carried out in 900 ml dissolution medium which was stirred at 75 rpm maintained at 37±0.2°C. The scheme of using the simulated fluids at different timing was as follows:

A tablet placed in dissolution media (900 ml, phosphate buffer, pH 6.8) at 37±0.2°C. Samples were withdrawn at different time interval and compensated with same amount of fresh dissolution medium. Volume of sample withdrawn was made up to 10ml phosphate buffer (pH 6.8). The samples withdrawn were assayed spectrophotometrically at 230.0 nm using UV visible spectrophotometer. The release of drug was calculated with the help of Standard curve of Irbesartan (Nagai *et al.,* 2022).

RESULTS AND DISCUSSION

Table 1: Formulation ingredients of various batches

F. Ingredients (mg)	F1	F2	F3	F4	F5	F6	F6	F8	F9
Irbesartan solid dispersion (Equivalent to 75mg)	300	300	300	300	300	300	300	300	300
SSG	6	12	18	-	-	-	-	-	-
CP	-	-	-	6	12	18			
CCS	-	-	-	-	-	-	6	12	18
Talc	5	5	5	5	5	5	5	5	5
Mg. Srearate	5	5	5	5	5	5	5	5	5
Lactose	5	5	5	5	5	5	5	5	5
Citric acid	14	8	2	14	8	2	14	8	2

Mannitol	5	5	5	5	5	5	5	5	5
Total wt.	340	340	340	340	340	340	340	340	340

Table 2: Percentage cumulative drug release of physical mixture

Parameter	**% Solubility enhancement**			
	Drug: PEG 400			
	1:1	**1:2**	**1:3**	**Pure Drug**
Absorbance	0.133	0.148	0.225	0.085
% Solubility Enhancement	140.00	155.78	236.84	----

Table 3: Results of drug content

Formulation	**Label claim**	**Amount found***	**Label claim (%)**
Physical mixture	10mg	9.98	99.98±0.12

Table 4: Results of pre-compressional parameters of Irbesartan

Formulation code	**Parameters**			
	Loose Bulk density(gm/ml)	**Tapped bulk density(gm/ml)**	**Carr's Index (%)**	**Hausner's Ratio**
F1	0.325	0.435	25.287	1.338
F2	0.324	0.436	25.688	1.346
F3	0.325	0.443	26.637	1.363
F4	0.345	0.465	25.806	1.348
F5	0.336	0.447	24.832	1.330
F6	0.315	0.418	24.641	1.327
F7	0.345	0.457	24.508	1.325
F8	0.345	0.485	28.866	1.406
F9	0.338	0.465	27.312	1.376

Table 5: Results of post-compression parameters of all formulations

F. Code	**Hardness test (kg/cm^2)**	**Friability (%)**	**Weight variation (%)**	**Thickness (mm)**	**Drug content (%)**
F1	3.4	0.852	340	2.3	98.85
F2	3.5	0.658	345	2.2	98.89
F3	3.6	0.745	333	2.1	96.65
F4	3.5	0.698	342	2.2	97.84
F5	3.2	0.845	345	2.4	97.12
F6	3.5	0.785	340	2.5	98.98
F7	3.6	0.658	346	2.4	99.65

F8	3.4	0.742	342	2.3	99.12
F9	3.5	0.854	341	2.4	98.85

Table 6: Results of *in vitro* disintegration time of all formulations

S. No.	Formulation code	Disintegration Time* (sec.)
1.	F1	89±3
2.	F2	85±4
3.	F3	78±5
4.	F4	65±7
5.	F5	62±4
6.	F6	58±3
7.	F7	39±2
8.	F8	42±4
9.	F9	48±3

Table 7: *In-vitro* drug release data for optimized formulation F7

Time (min)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative*% Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
1	1	0	45.56±0.45	1.659	54.44	1.736
5	2.24	0.698	78.89±0.54	1.897	21.11	1.324
10	3.16	1	98.58±0.65	1.994	1.42	0.152

Table 8: Regression analysis data

Batch	Zero Order	First Order
	R^2	R^2
F7	0.955	0.958

CONCLUSION

In conclusion, the formulation and development of novel controlled-release transdermal patches of Bupranolol present promising potential for enhancing the treatment of hypertension and related cardiovascular conditions. The study demonstrated successful enhancement of solubility, accurate drug content, and appropriate pre- and post-compressional parameters, ensuring the quality, uniformity, and performance of the formulations. Formulation F7 emerged as the optimized formulation, exhibiting rapid disintegration,

sustained drug release, and favorable release kinetics profiles. These findings highlight the feasibility of utilizing transdermal patches as a viable drug delivery system for Bupranolol, offering improved patient compliance, enhanced bioavailability, and therapeutic efficacy. Further studies, including in vivo evaluations and clinical trials, are warranted to validate the pharmacokinetic and pharmacodynamic properties, safety, and effectiveness of the developed transdermal patches, paving the way for their potential clinical applications in the management of hypertension.

DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

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