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Development and Characterization of Isradipine Compression Coated Controlled Release Mini-Tablets

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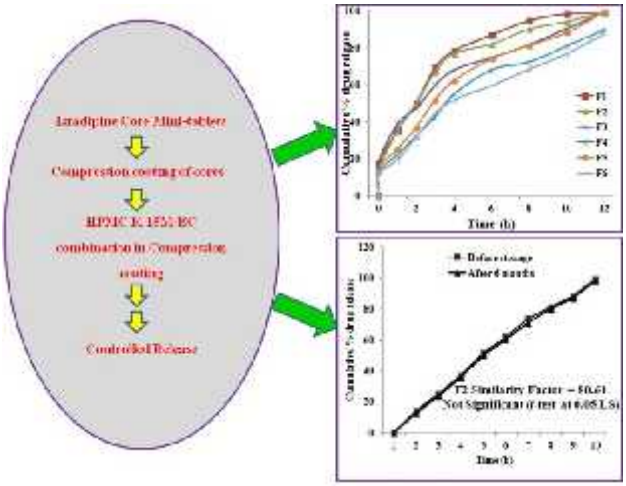
Graphical Abstract



Abstract

The intent of present study is to develop the Isradipine controlled release tablets through compression coating of mini-tablets with the help of hydrophilic and hydrophobic polymers. Isradipine mini-tablets were prepared by direct compression method and compression coated using various concentrations of HPMC K15M, Ethyl cellulose and combination of Ethyl cellulose and HPMC K15M. The prepared tablets were characterized for weight variation, hardness, friability and drug content. Formulations were evaluated for the release of isradipine over a period of 12 h using type-II USP XXIV standard dissolution apparatus in 6.8 pH phosphate buffer. From the in vitro drug release studies, F5 tablets showed 99.43±0.72% drug release in 12 h and it followed zero order drug release. The mean dissolution time of all formulations was found to be 4.48 – 10.52 h and it was higher for formulations with ethyl cellulose when compared to HPMC K 15M due to its hydrophobic nature. Time in hours to take 80% drug release explained the ability of prolonged release and they were found to be 10.2 h for best formulation F5. From the stability study, similarity factor (f2) was found as 80.61, which is more than 50 indicates similarity between the dissolution profile before and after storage. Hence the development of isradipine compression coated mini-tablets is a promising way to control the drug release as per therapeutic requirement.

Key Words: *Controlled release; Direct compression; Hydrophilic; Hydrophobic; Mini-tablets;*

Introduction

Present pharmaceutical research is focusing not only on the development of various novel drug delivery systems but also on the new technologies for conventional oral solid drug delivery systems [1]. One of such technologies is development of mini-tablets that has the advantages of both tablets (ease of manufacturing, packaging, storage and minimum scalability problems) as well as multi-particulate systems. Mini-tablets are small tablets that are typically filled into a capsule, or occasionally further compressed into large tablets. These are beginning to emerge as a new variation in the oral solid dosage forms, which offer formulation flexibility [2]. Additional benefits of mini-tablets include excellent size uniformity, regular shape and a smooth surface, thereby offering an excellent substrate for coating with different polymeric systems. Like other multi unit dosage forms several mini-tablets can be filled into either hard capsules or compacted into bigger tablets that, after disintegration, release these subunits as multiple dosage forms [3].

In the present study isradipine is used as the model drug. Isradipine is a di-hydro pyridine calcium channel blocker and inhibits calcium flux into cardiac and smooth muscle [4]. Due to its short half-life and very low bioavailability, the present work describes such delivery system, which will improve the biological half-life as well as bioavailability [5]. In this study, isradipine controlled release tablets were prepared by compression coating of mini-tablets with the help of hydrophilic and hydrophobic polymers. Isradipine mini-tablets were prepared by direct compression method and compression coated using various concentrations of HPMC K15M, Ethyl cellulose and combination of Ethyl cellulose and HPMC K15M.

Materials

Isradipine, Ethyl cellulose and HPMC K15M are obtained as a gift sample from KP Laboratories, Hyderabad, India. All other chemicals used were of analytical grade.

Experimental Methods

Preparation of isradipine core mini-tablets and compression coated tablets

Isradipine core mini-tablets were prepared by direct compression method. Isradipine and excipients other than glidant and lubricant were accurately weighed, passed through 60 # sieve, then blended for 5-10 min in poly bag, lubricated and finally resultant mixture was converted to tablets with 4 mm round flat punches on rotary punching machine at slow speed (Table 1). The prepared mini-tablets were compression coated by direct compression method with 6 mm round flat punches using various compositions given in Table 2. Compression coating of core mini-tablets was done by placing half of the coating material in die cavity, then cautious placing of mini-tablets in middle and finally placing the remaining half of coating material [1].

Table 1 Formulation of isradipine mini-tablet cores

Ingredients	Quantity (mg)
Isradipine	10
Spray dried lactose	22.5
Crosspovidone	5.0
Sodium lauryl sulphate	1.0
Talc	1.0
Magnesium stearate	0.5
Core weight	50

Table 2 Formulation of compression coated tablets using isradipine mini-tablet cores

Formulation	Core tablet (mg)	HPMC K15M (mg)	Ethyl Cellulose (mg)	Total tablet weight (mg)
F1	50	20	-	120
F2	50	40	-	120
F3	50	-	20	120
F4	50	-	40	120
F5	50	15	15	120
F6	50	20	20	120

Evaluation of compression coated tablets

The prepared tablets were studied for their physical properties like weight variation, hardness and friability. For estimating weight variation, 20 tablets of each formulation were weighed using an Electronic weighing balance (AW 120, Shimadzu Corporation, Japan). The strength of tablet is expressed by measuring hardness and friability. The hardness of ten tablets was measured using Monsanto tablet hardness tester. Friability was determined on ten tablets in a Roche friabilator (Electro lab, Mumbai, India) for 4 min at 25 rpm. For estimation of drug content, ten tablets were crushed, and the aliquot of powder equivalent to 50 mg of drug was dissolved in suitable quantity of pH 6.8 phosphate buffer solution. Solution was filtered and diluted and drug content determined by UV-Visible spectrophotometer (Systronics 2202, India) at 332 nm. The drug concentration was calculated from the calibration curve.

***In vitro* drug release study**

Drug release was assessed by dissolution test under the following conditions: n=3, USP type II dissolution apparatus (paddle method) at 50 rpm in 900 ml 6.8 pH phosphate buffer for 12 h. An aliquot (5ml) was withdrawn at specific time intervals and replaced with the same volume of pre-warmed (37°C ± 0.5°C) fresh dissolution medium. The samples were filtered through Whatman filter paper and analyzed by UV-visible spectrophotometer.

To elucidate the drug release pattern and mechanism from the from the prepared compression coated tablets, the data obtained from the *in vitro* dissolution studies was integrated to zero order, first order and Higuchi models and Koresmeyer–Peppas model [6-7]. Then the dissolution data was also used to calculate the mean dissolution time (MDT- the sum of different release fraction periods during dissolution studies divided by the initial loading dose), T10% and T80% (time in hours to take 10% and 80% drug release, respectively) to elucidate the drug release from compression-coated tablets [8].

Stability studies

In stability studies, three replicates of F5 compression coated tablets were sealed in aluminum coated inside with polyethylene pack and stored at 40±2 ^{o}C and 75±5% RH in the humidity chamber for six months [9]. Samples were collected after six months of storage and estimated for the drug content and *in vitro* dissolution rate. Then to prove the stability of dosage form, the similarity factor (f_2) was calculated between dissolution rates of optimized tablets before and after storage [10-11]. At this point, the data was statistically analyzed using paired *t*-test to test the significance of difference at level of significance 0.05.

Results and Discussion

Evaluation of compression coated tablets

From the weight variation test, it was found that the average weights of various batches were 119.32±1.94 to 121.85±2.12 mg. The tablet hardness and friability were found to be 4.30±0.17 to 4.43±0.15 kg/cm^2 and 0.48 to 0.32% among various batches of tablets. Drug content of prepared tablets was from 99.02±0.44% to 100.48±1.73%. Form these results it is concluded that the compression coated tablets were complied with the Indian pharmacopoeial standards (Table 3).

Table 3 Physical properties of isradipine compression coated tablets

Formulation	Weight variation* (mg)	Hardness† (Kg/cm^2)	Friability (%)	Drug content‡ (%)
F1	119.32±1.94	4.39±0.62	0.48	99.74±1.26
F2	120.21±2.86	4.30±0.17	0.42	99.02±0.44
F3	120.29±2.57	4.32±0.36	0.46	100.02±1.18
F4	121.85±2.12	4.41±0.42	0.42	99.91±1.42
F5	121.12±1.94	4.38±0.16	0.36	100.48±1.73
F6	120.18±2.16	4.43±0.15	0.32	99.56±1.32

* All values represent mean ± standard deviation, n=20; † All values represent mean ± standard deviation, n=6; ‡ All values represent mean ± standard deviation, n=3

In vitro dissolution studies

In vitro drug release form prepared compression coated tablets were expressed in Figure 1. In the present study, HPMC formulations were shown initial burst release when compared to ethyl cellulose formulations due to its hydrophilic nature. But the formulations containing hydrophobic ethyl cellulose were shown more sustained release than HPMC. In case of F5 and F6 formulations, due to combination of both hydrophilic HPMC K15M and hydrophobic ethyl cellulose, they were shown better controlled release. From these studies F5 formulation is the best in showing 12 h controlled release in low polymer concentration, hence it was selected as the best formulation.

For compression coated tablets the values of K, and r^2 (correlation coefficient of the regression analysis) of zero order, first order and Higuchi models and MDT, T10% and T80% were given in Table 4. The drug release kinetics revealed high correlation coefficient values for zero order than first order indicating that the drug release from compression coated tablets followed zero order patterns. Zero order release was also observed in a study with 5-fluorouracil using HPMC in the compression coat [12]. The n values calculated for different formulations indicating a supercase-II transport. The MDT and T80% values of F5 formulation were proved the controlled release of drug for 12 h.

Table 4 Drug release kinetics parameters of F5 compression coated tablets

Formulation Code	Zero order (R^2)	First order (R^2)	Higuchi (R^2)	Koresmeyer & Peppas (R^2)	Peppas (n)	MDT (h)	T10% (h)	T80% (h)
F5	0.9942	0.8421	0.9532	0.9918	1.2137	8.34	4.48	10.52

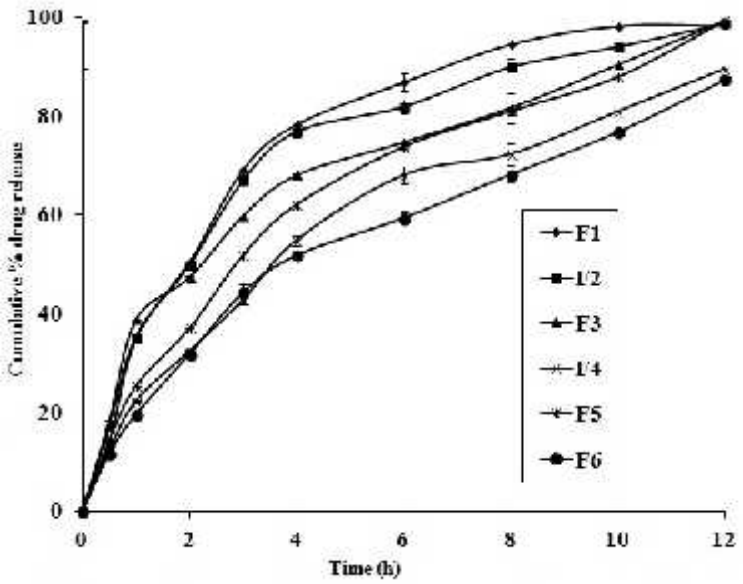


Figure 1 In vitro dissolution studies of compression coated mini-tablets

Stability studies

Figure 2 was shown the results of stability studies of F5 compression coated tablets. The data found was subjected to statistical analysis and proved that they were not significantly different from each other (P<0.05). From the stability study, similarity factor ($f2$) was found as 80.61, which is more than 50 indicates similarity between the dissolution profile before and after storage.

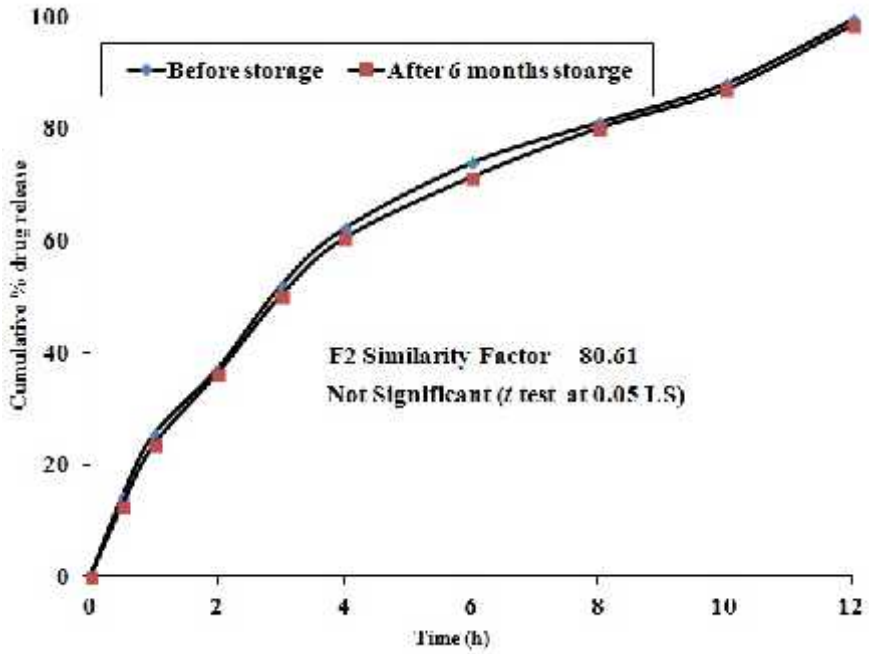


Figure 2 Stability studies of F5 compression coated tablets

Conclusions

The present study was investigated to formulate isradipine controlled release compression coated mini-tablets with addition of release retarding polymers like HPMC K15 M, ethyl cellulose and combination of above both. From the *in vitro* drug release studies, F5 formulation containing combination of both polymers was the best formulation and had shown controlled release for 12 h. The release process depends on swelling, relaxation and erosion of polymer with zero order release kinetics. Stability studies proved the obtained the stability of formulation. Further the efficacy of the developed formulations has to be assessed by pharmacokinetic studies.

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