

DEVELOPMENT AND *IN-VITRO* EVALUATION OF CONTROLLED RELEASE MATRIX TABLETS OF ISRADIPINE EMPLOYING VARIOUS NATURAL POLYMERS

SUBRAMANYA GUPTA*¹, KARTHEEK SIRIPURAPU², RAMYA SWATHI M³, MADHURI KALLURI⁴, SRINIVASA RAO M⁵, B. KISHORE KUMAR REDDY⁶

¹Department of Pharmaceutics, School of Pharmaceutical Sciences and Technologies, JNTUK, Kakinada, A.P., India, ²Department of Formulation Development, Aizant laboratories Ltd., Hyderabad, ^{3,6}Department of Pharmaceutics, A.K.R.G College of Pharmacy, Nallegerla, ⁴Faculty of Pharmaceutics, K.J.R. College of Pharmacy, Burugupudi, ⁵Department of Quality Assurance, Beloorbayir biotech Ltd. Tumkur, Karnataka. Email: sriintegrity@gmail.com

Received: 13 Feb 2014, Revised and Accepted: 30 Apr 2014

ABSTRACT

Objective: The present investigation was aimed at designing controlled release matrix tablets of isradipine, using various natural polymers like guar gum, karaya gum, xanthan gum and veegum, individually and in combinations of various concentrations, to produce controlled release of isradipine in order to improve the efficacy and patient compliance and to compare the drug release profiles of optimized formulation and commercial formulation by similarity and difference factors.

Method: The drug excipient compatibility studies were performed by FTIR spectroscopy. The controlled release matrix tablets were prepared by direct compression method. The prepared tablets were evaluated for physicochemical characteristics and *in-vitro* dissolution studies. Isradipine release from optimized formulation was compared with commercial product by similarity factor and difference factors.

Results: The compatibility of the drug with excipients was confirmed by FTIR study. The prepared tablets exhibited satisfactory physicochemical characteristics. The *in-vitro* drug release studies revealed that the drug release was sustained up to 24hrs for formulation F9 containing equal proportions of xanthan gum and karaya gum. The drug release from the formulation was found to be zero order. Using Higuchi's model and the Korsmeyer equation, the drug release mechanism from the controlled release tablets was found to be Anomalous (non-Fickian) diffusion. The values of difference factor, f_1 and similarity factor, f_2 was found to be 1.74 and 63.38 indicating similarity between drug release profiles of optimized formulation and reference product (Dynacirc CR 10mg).

Conclusion: Natural polymers were found to be a promising approach for the formulation of controlled release matrix tablets of isradipine.

Keywords: Similarity factor, Difference factor, Direct compression, Zero order.

INTRODUCTION

The oral drug administration has been the predominant route for drug delivery. It is known to be the most popular route of drug administration due to the fact that the gastrointestinal physiology offers more flexibility in dosage form design than most other routes [1,2]. A major challenge for the pharmaceutical industry in drug development is to produce safe and efficient drugs, therefore properties of drugs and the way in which they are delivered must be optimized [3,4]. In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of controlled drug delivery system that could revolutionize method of medication and provide a number of therapeutic benefits [5]. Controlled release technology now forms the essence of modern and future drug delivery system for last several decades in terms of clinical efficacy and patient compliances [6]. The natural polymers are more superior to the synthetic polymers in respect of their highly organized macroscopic and molecular structure. This adds to their strength and biocompatibility. Moreover, their low toxicity and excellent biodegradability have also attracted researchers to pay attention towards the widespread application of natural polymers [7].

The release rate will be controlled depending upon the type and concentration of the polymer that swells, leads to the diffusion and erosion of the drug [8-10].

The present investigation was aimed at designing controlled release matrix tablets of Isradipine, using various natural polymers like guar gum, karaya gum, xanthan gum and veegum, individually and in combinations of various concentrations, to produce a controlled release of isradipine in order to improve the efficacy and patient compliance and to compare the drug release profiles of optimized

formulation and commercial formulation by similarity and difference factors.

Isradipine belongs to the dihydropyridine (DHP) class of calcium channel blockers (CCBs), the most widely used class of CCBs. It is used for the treatment of mild or moderate hypertension, in prophylactic treatment of angina pectoris and Raynaud's syndrome. It comes under BCS class II, low solubility, low bioavailability (approximately 15-24%), and shorter half-life [11,12]. By considering above facts, isradipine matrix tablets employing various natural polymers were designed and characterized for controlled release in order to improve the patient compliance in such a way that it reduces dosing frequency, reduces side effects and increases the patient compliance [13, 14].

MATERIALS AND METHODS

Materials

Isradipine and Avicel PH 102 were obtained as gift samples from Aurobindo Pharma, Hyd. Guar gum, veegum, karaya gum, xanthan gum, magnesium stearate and talc were procured from SD Fine Chemicals, Mumbai. All other ingredients used were of analytical grade.

Methods

Drug-Excipient Compatibility Studies:

The pure drug and drug-excipients physical mixture were subjected to FTIR studies. The pure drug and its combination with excipients were separately mixed with IR grade potassium bromide in a ratio (1:100) and the pellets were prepared by applying 10 metric tons of pressure in a hydraulic press. The pellets were then scanned over the range of 4000-400 cm^{-1} in FTIR instrument (Bruker ATR Alpha-e, Germany).

Formulation of Isradipine Controlled Release Matrix Tablets

Tablets containing 10 mg of isradipine were prepared, according to the formulae given in Table 1, by direct compression. The respective powders, namely isradipine, release-retarding polymer(s) (guar gum, xanthan gum, veegum and karaya gum) were passed through sieve no. 20, separately. Mixing of powders was carried out using a pestle and mortar for 10 min. Avicel PH 102 and magnesium

stearate were then added to the mixed powders. Mixing was continued for another 3 min. Finally, 150 mg of each mixture were weighed and fed manually into the die of a single punch tableting machine (Royal artist, Bombay, India), equipped with flat-faced punches (8.0 mm), to produce the desired tablets. The hardness of the tablets was adjusted at 5 kg/cm² using a Monsanto hardness tester (Monsanto Chemical, St. Louis, MO).

Table 1: Formulae for Isradipine Controlled Release Matrix Tablets

Ingredients mg/tab	Formulation								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Isradipine	10	10	10	10	10	10	10	10	10
Veegum	37.5	-	-	-	45	-	-	-	-
Guar gum	-	37.5	-	-	-	45	-	-	-
Xanthangum	-	-	37.5	-	-	-	45	-	22.5
Karaya gum	-	-	-	37.5	-	-	-	45	22.5
MCC	98	98	98	98	90.5	90.5	90.5	90.5	90.5
Mg. stearate	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25
Talc	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25
Total Weight	150	150	150	150	150	150	150	150	150

In-vitro evaluation of the prepared matrix tablets

Tablet Weight Variation

Twenty tablets were randomly selected and accurately weighed. Results are expressed as mean values \pm SD.

Tablet Thickness

A vernier caliper (For-bro Engineers, Mumbai, India) was used to determine thickness of 10 randomly selected tablets. Results are expressed as mean values \pm SD.

Friability Test:

Ten tablets were randomly selected and placed in the drum of a tablet friability test apparatus (Roche). The drum was adjusted to rotate 100 times in 4 min. The tablets were removed, de-dusted and accurately weighed. The percent weight loss was calculated.

Drug content uniformity

Ten tablets were individually weighed and crushed. A quantity of powder equivalent to the dose of one tablet (10 mg) was extracted in 100 ml of methanol. The solution was filtered through a cellulose acetate membrane (0.45 μ m). The solution was then suitably diluted with 0.2% lauryl dimethyl amine oxide in water and the drug content was determined by UV spectroscopy (1601-PC Double beam spectrometer, Shimadzu, Kyoto, Japan) at a wavelength of at 285 nm.

Drug Release Studies

Drug release studies of the prepared matrix tablets as well as the commercially available Dynacirc CR 10mg tablets were performed, in triplicate, in a USP Dissolution Rate Test Apparatus, type-II (Paddle method) (M/s Labindia Disso 8000) at 37 \pm 0.5 C. The paddles rotated at a speed of 50 rpm. The tablets were placed into 900 ml of 0.2% lauryl dimethyl amine oxide in water. Aliquots of 5 ml were withdrawn from the dissolution medium at different time intervals over a period of 24hr and filtered through a cellulose acetate membrane (0.45 μ m). Samples were suitably diluted and assayed for Isradipine content at 285 nm by using an UV-spectrophotometer. The samples of dissolution fluid withdrawn at each time were replaced with fresh fluid at the same temperature.

Kinetic modeling of drug release profiles

The drug release profiles of all formulae in 0.2% lauryl dimethyl amine oxide in water were fitted to zero-order, first-order, Higuchi [15] and Korsmeyer-Peppas [16] kinetic models. The model with the highest correlation coefficient was considered to be the best fitting one.

Comparison of drug release profile of optimized formulation with commercial product

The drug release profile of optimized formulation was compared with the commercially available formulation Dynacirc CR 10mg statistically by difference factor, f1 and similarity factor, f2 [17].

$$f1 = \left\{ \frac{\sum_{t=1}^n |Rt - Tt|}{\sum_{t=1}^n Rt} \right\} \times 100$$

$$f2 = 50 \times \log_{10} \left[1 + \left(\frac{1}{n} \sum_{t=1}^n (Rt - Tt)^2 \right)^{-0.5} \right] \times 100$$

RESULTS AND DISCUSSION

FTIR Study

The FTIR spectra of Isradipine and powder of isradipine-exipients physical mixture were shown in Fig:1.

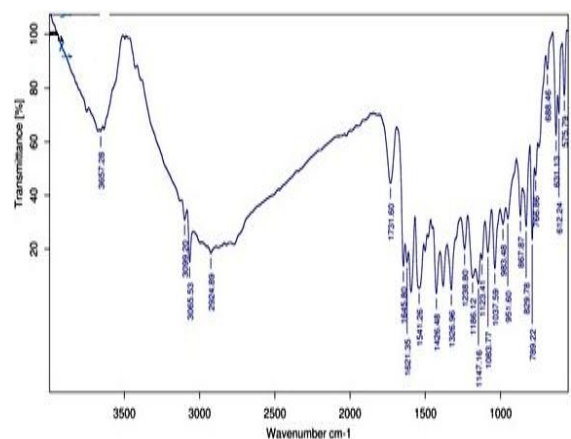


Fig. 1: FTIR Spectra of Isradipine

The FTIR spectra isradipine pure drug and isradipine-exipients physical mixture showed the following characteristic peaks, 789 cm⁻¹ due to C-H stretching vibrations, 1732 cm⁻¹ due to C=O stretching vibrations, 1541 cm⁻¹ due to CH-CH₂CH₂ stretching vibrations, 2876 cm⁻¹ due to O-CH₃ stretching vibrations, 1670 cm⁻¹ due to C=C stretching vibrations and 1645 cm⁻¹ due to C-O-C bending vibrations. Indicating all functional groups are intact. Hence, it is a confirmation that no chemical reactions have taken place amongst any of the constituents in the formulation.

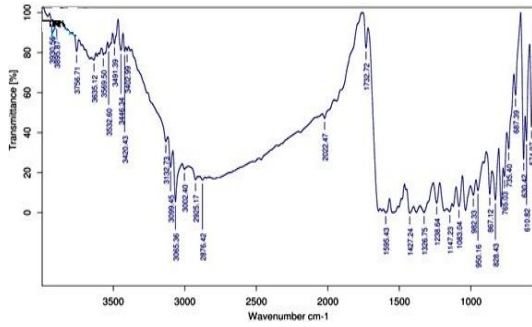


Fig. 2: FTIR Spectra of Isradipine-Excipients Physical Mixture

Physicochemical Properties

Isradipine controlled release matrix tablets were developed employing natural matrix forming polymers guar gum, veegum,

karaya gum and xanthan gum by the direct compression method. The incorporation of microcrystalline cellulose "Avicel PH 102" in the designed systems was suggested to impart superior flow and enhance powder compaction in direct compression.

The physicochemical properties of the tablets are summarized in Table 2. The thickness of all tablet batches ranged from 2.75 ± 1.31 to 2.96 ± 0.14 mm. All the tablet formulae showed acceptable physicochemical properties and complied with the pharmacopoeial specifications for weight variation, drug content and friability. The weight of the tablets ranged from 148.68 to 153.01 mg. All the prepared formulae meet the USP 27 [18] requirements for weight variation tolerance; CV% was less than 2%.

Drug uniformity results were found to be good among different batches; the percentage of drug content ranged from 98.40% to 100.50%. The percentage friability for all formulae was less than 1%, indicating good mechanical resistance.

Table 2: Physicochemical Properties of the Isradipine Matrix Tablets

Formulation	Thickness (mm) Mean \pm SD	Tablet weight (mg) Mean \pm SD	Friability (%) Mean \pm SD	Drug Content (%) Mean \pm SD
F1	2.88 \pm 0.16	150.12 \pm 1.56	0.163 \pm 0.13	100.5 \pm 0.5
F2	2.89 \pm 0.18	153.09 \pm 2.32	0.220 \pm 0.41	98.4 \pm 1.26
F3	2.85 \pm 0.32	150.15 \pm 2.65	0.320 \pm 0.21	99.7 \pm 0.98
F4	2.90 \pm 0.03	148.67 \pm 2.13	0.262 \pm 0.12	99.8 \pm 0.74
F5	2.93 \pm 0.16	151.05 \pm 2.75	0.420 \pm 0.35	100.9 \pm 1.23
F6	2.96 \pm 0.14	153.01 \pm 2.47	0.490 \pm 0.21	99.9 \pm 1.45
F7	2.91 \pm 0.16	150.11 \pm 3.23	0.341 \pm 0.013	99.9 \pm 0.89
F8	2.75 \pm 1.31	149.82 \pm 3.34	0.549 \pm 0.11	100.1 \pm 0.76
F9	2.77 \pm 0.58	148.71 \pm 3.56	0.269 \pm 0.014	100.5 \pm 0.76

In - Vitro Drug Release Studies

Isradipine release from prepared controlled release matrix tablets and also Reference Product (Dyanacirc CR 10mg) were studied in 0.2% lauryl dimethyl amine oxide in water over 24hr. The drug release profiles depends on the concentration of retardant polymer present in the matrix tablets. The Drug release profiles are shown in Figure 3. Out of all 9 formulations only F9 can sustain drug release up to 24hr and also satisfies official specifications of USP for controlled release tablets i.e. NMT 20% of the labelled amount of drug is getting released in first 1 hr, NLT 45% & NMT 70% of the labelled amount of drug in 8hrs & NLT 75% of the labelled amount of isradipine in 24hrs.

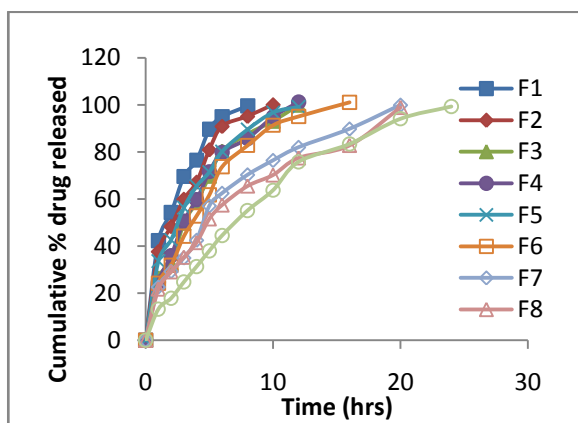


Fig. 3: Drug release of Isradipine controlled release matrix tablets

The drug release data were analyzed as per zero order, first order, Higuchi equation and Korsmeyer Peppas equation models to know the order and mechanism of drug release from prepared matrix tablets.

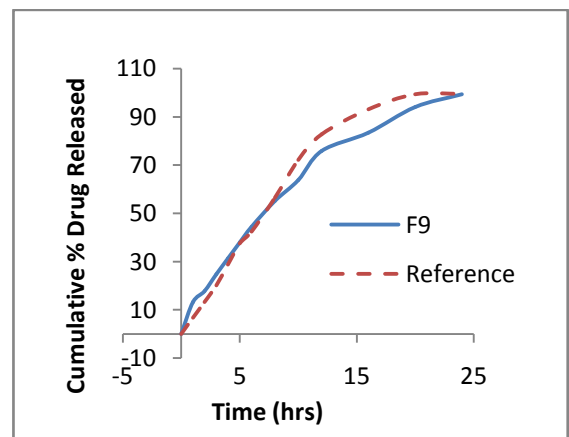


Fig. 4: Comparison of Drug release of Isradipine optimized formulation and reference product

When the release data were analyzed as per zero and first order models the correlation coefficient (R^2) values were relatively higher in the zero order model with all Matrix tablets formulated indicating that the drug release from all these tablets followed zero order kinetics. Isradipine drug release data were also obeyed Higuchi and Peppas models with R^2 values greater than 0.9. When percentage drug released was plotted against $\sqrt{\text{time}}$, linear regressions with ' R^2 ' > 0.947 were observed with all Matrix tablets prepared indicating that the drug release from all these formulations was diffusion controlled. Korsmeyer and Peppas equation superposes two apparently independent mechanisms of drug transport, Fickian diffusion and a case-II transport, for the description of drug release from a swelling polymer. For a matrix tablet, when n takes the value of 0.45 it indicates diffusion-controlled drug release and for the value 0.89, it indicates swelling-controlled drug release. Values of ' n '

between 0.45 and 0.89 can be regarded as an indicator for both the phenomena (anomalous transport). The values of the diffusion exponent (n) with the corresponding correlation coefficients for all the formulations were shown in Table 3. The 'n' values of various formulations were found to be between 0.45 and 0.89, indicating anomalous transport. The relative

complexity of the prepared formulations may indicate that the drug release is controlled by more than one process; a coupling of diffusion and erosion [19]. The values of difference factor, f1 and similarity factor, f2 was found to be 1.74 and 63.38 indicating similarity between drug release profiles of optimized formulation and reference product.

Table 3: Mathematical Modelling and Release Kinetics of Isradipine Controlled Release Matrix Tablets

Formulation	Zero order correlation coefficient R ²	First order correlation coefficient R ²	Higuchi's plot correlation coefficient R ²	Korsmeyer-Peppas plots		Order of release
				Correlation coefficient R ²	Diffusional exponent (n)	
F1	0.988	0.935	0.952	0.982	0.807	Non-Fickian
F2	0.982	0.932	0.991	0.992	0.794	Non-Fickian
F3	0.979	0.921	0.947	0.936	0.729	Non-Fickian
F4	0.972	0.899	0.949	0.937	0.756	Non-Fickian
F5	0.984	0.970	0.971	0.974	0.761	Non-Fickian
F6	0.973	0.961	0.976	0.981	0.729	Non-Fickian
F7	0.972	0.898	0.967	0.991	0.774	Non-Fickian
F8	0.965	0.959	0.966	0.984	0.751	Non-Fickian
F9	0.963	0.931	0.981	0.951	0.797	Non-Fickian
Reference	0.978	0.938	0.953	0.973	0.97	Zero order

The drug release profiles comparison between the optimized formulation and the reference product was shown on the Fig. 4 The optimized formulation was statistically compared to the reference formulation by differentiating factor, f2 and similarity factor, f1.

CONCLUSION

Controlled release matrix tablets of Isradipine were successfully developed employing four different natural polymers. Among all the formulations, slow and spread over drug release for 24hrs was observed in formulation F9. Hence F9 was taken as optimized formulation. The optimized formulation was found similar to the reference product (Dynacirc CR 10mg), which was confirmed by statistical analysis. From the above results, F9 was found suitable for controlled release.

REFERENCES

- Chen X. Challenges and new technologies of oral controlled release. In: Wen H, Park K, eds. Oral controlled release formulation design and drug delivery: Theory to Practice. 2010; 16:257-277.
- Maderuelo C, Zarzuelo A and Lanao JM.. Critical factors in the release of drugs from sustained release hydrophilic matrices. J. Control. Release. 2011; 154:2-19.
- Gupta PK and Robinson JR.. Oral controlled release delivery. In: Kyodenius A. eds. Treatise on Controlled Drug Delivery. New York: Marcel Dekker. 1992.
- Tongwen X and Binglin H. Mechanism of sustained drug release in diffusion controlled polymer matrix application of percolation theory. Int. J. Pharma. 1998; 170:139-149.
- Hemmani M, Patel U, Patel G, Daslaniya D, Shah A, Bhimani B. Matrix tablets: a tool of controlled drug delivery. American J. of PharmTech Research. 2011; 1(4):127-143.
- George M, Grass IV, Robinson JR. Sustained and controlled release drug delivery systems. In: Banker GS, Rhodes CT, eds. Modern Pharmaceutics. 1989; 2:575 - 609.
- Kumar, Shobhit, Satish Kumar Gupta. Natural polymers, gums and mucilages as excipients in drug delivery. Polim. Med. 2011; 3(4): 191-197.
- Uhrich, Kathryn E., et al. Polymeric systems for controlled drug release. Chemical Reviews. 1999; 99(11) :3181-3198.
- Langer, Robert, Nikolaos Peppas. Chemical and physical structure of polymers as carriers for controlled release of bioactive agents: a review. Journal of Macromolecular Science-Reviews in Macromolecular Chemistry and Physics. 1983; 23(1): 61-126.
- Sweetman SC. In: Martindale, The Complete Drug Reference. 33rd ed. Great Britain: Pharmaceutical Press; 2002:645-648.
- Fitton, Andrew, Paul Benfield. Isradipine. Drugs. 1990; 40(1): 31-74.
- <http://www.drugbank.ca/drugs/DB00270>
- Hadi Mohd Abdul, Raghavendra Rao NG, Firangi Sunil. Mini tablets technology: an overview. Am J Pharmtech Res. 2012; 2:128-150.
- Hadi Mohd Abdul, Raghavendra Rao NG. Novel techniques in formulations: an overview. World J Pharm Res. 2012; 1:1-17.
- T. Higuchi: Mechanism of sustained action medication. J. Pharm. Sci. 1963; 52: 1145-1149.
- R.W. Korsmeyer, R. Gurny, E. Docler, P. Buri, N.A. Peppas: Mechanism of solute release from porous hydrophilic polymers. Int. J. Pharm. 1983; 15: 25-35.
- Shah, Vinod P., et al. In vitro dissolution profile comparison—statistics and analysis of the similarity factor, f2. Pharmaceutical research. 1998; 15(6): 889-896.
- United States Pharmacopeia 27 and National Formulary 22, Asian Edition, United States Pharmacopeial convention, Inc., Rockville, 2004 (electronic version).
- M. Srinivasa Rao, K.S.N. Madhuri, G. Vijaya Kumar: Formulation and evaluation of controlled release floating tablets of lamivudine employing HPMC K4M and sodium alginate. Int. J. Pharm. Sci. & Res. 2013; 4 (1): 396-40.