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Studies on the Development of Celecoxib Transdermal Patches

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Abstract: Celecoxib,[chemically designated as 4-[5-(4methyl phenyl)-3-(trifluoromethyl)-1H-pyrazol1-1-yl] benzene sulphonamide] a diaryl substituted pyrazole, is a non steroidal anti-inflammatory drug that exhibits anti-inflammatory, analgesic and antipyretic activities, especially in arthritis. Since celecoxib has gastro intestinal side effects including abdominal pain, dyspepsia ,diarrhea and ulcers and it is subjected to an extensive and highly intersubject variable hepatic first pass metabolism by p450(CYP)2c9 and it has low bioavailability due to its lipophillic nature. Different matrix type transdermal patches incorporating celecoxib with an objective to overcome all the disadvantages mentioned and to study the effect of polymers on transdermal release of the drugs were prepared. The polymers selected were hydroxy propyl methyl cellulose (15cps), polyvinyl pyrrolidone (15cps), Methyl cellulose (15cps). The patches were formulated using combination of polymers and dibutyl phthalate 30%w/w, as plasticizer. The physiochemical evaluation of polymer matrices was performed for suitability. The interaction among various components of the matrices was studied by infrared spectroscopy and differential scanning calorimetry. *In vitro* dissolution studies were carried out in phosphate buffer pH 7.4 using commercial semi permeable membrane. *Ex vivo* drug diffusion study was carried out using various biological membranes such as rat skin, guinea pig skin and pig ear skin in order to select the best biological system which has good correlation with *in vitro* release. The results indicated that maximum release (85%) was obtained in 24h using rat skin which has the best correlation with human skin as per the earlier studies.
Key words: Celecoxib, arthritis, transdermal drug delivery system, *ex vivo* diffusion, *in vitro ex vivo* correlation.

INTRODUCTION

Transdermal delivery constitutes one of the most important route for novel drug delivery system (NDDS). Transdermal delivery of drug offers several advantages over conventional delivery methods including oral and injection methods. Transdermal delivery, that traditionally uses a patch containing drug substance pressed on to the skin, is non-invasive, convenient, painless and can avoid gastro intestinal toxicity (e.g. peptic ulcer disease) and the hepatic first pass metabolism.

Celecoxib is an anti inflammatory, analgesic and antipyretic drug used in the treatment of rheumatoid arthritis, osteo arthritis[1]. The mechanism of action of celecoxib is believed to be due to inhibition of prostaglandin synthesis, primarily via inhibition of cyclooxygenase-2. It has been shown that at

therapeutic concentration in humans, celecoxib does not inhibit Cox-l isoenzyme. Celecoxib is lipophillic and is almost completely absorbed after the oral administration. However much of the drug is metabolized by the liver during its first passage through the portal circulation. So the increased dose may be required over time. Celecoxib has gastro intestinal side effects such as abdominal pain, dyspepsia, diarrhea and fewer intestinal ulcers in patients treated with cox-2 inhibitors. The absorption of celecoxib given in capsules was delayed by food although systemic exposure increased by 3-5fold. Celecoxib exhibit poor flow properties and compressibility. Hence transdermal therapeutic system is preferred over conventional dosage forms to achieve prolonged blood level and the physicochemical properties such as low molecular weight (381.4) and low melting point (155°) makes this a suitable candidate for administration by the transdermal route.

MATERIAL AND METHODS

MATERIAL

Celecoxib was obtained as gift sample from brown and burk pharmaceuticals, pvt. ltd, bangalore. Polyvinyl pyrrolidone (PVP) was obtained from BPRL, Bangalore. Hydroxy propyl methyl cellulose (HPMC) and methyl cellulose (MC) from arco labs, ltd, bangalore. Dibutyl phthalate, ethanol, chloroform, dichloro methane were purchased from the local source. The drug samples were characterized by UV[2, 3], IR methods by using UV-Visible spectrophotometer, schimadzu, [model no.1201], Jasco FT/IR-140 fourier transform infrared spectrometer

PREPARATION OF THE DRUG CONTAINING POLYMER MATRICES

Films composed of different polymers HPMC, MC and PVP were prepared in suitable solvent systems such as mixtures of ethanol and dichloromethane for HPMC, ethanol and chloroform for MC and PVP was dissolved in ethanol. Dibutyl pthalate (30%w/w of dry weight of polymers) as plasticizer was added with continuous stirring using teflon magnetic bead placed in magnetic stirrer. Drug (one single oral dose of the drug) was added to the polymer solutions and stirred continuously for an hour and the solutions were casted on the backing membrane (Aluminum foil) and dried in a desiccator at room temperature (**Table1).** Backing membrane was prepared by wrapping aluminum foil over the teflon mold. The films were then packed in aluminum foil and stored in a desiccator until further evaluation.

DETERMINATION OF PERCENT MOISTURE ABSORPTION

The films were accurately weighed and placed in a dessicator containing 100ml of saturated solution of aluminium chloride which maintains 79.50% RH. After 3 days the films were taken & weighed. The percent moisture absorption was calculated using the formula

Present moisture absorption=Final weight – Initial weight / Initial weight X100

TABLE1: COMPOSITION OF VARIOUS FORMULATIONS OF CELECOXIB TRANSDERMAL PATCHES

Formulation code	MC	HPMC	PVP
F1	-	-	1
F2	-	1	-
F3	1	-	-
F4	-	0.75	0.25
F5	-	0.25	0.75
F6	-	0.50	0.50
F7	0.75	-	0.25
F8	0.25	-	0.75
F9	0.50	-	0.50
F10	0.33	0.33	0.33

Abbreviations used: MC-Methyl cellulose; HPMC-Hydroxy propyl methyl cellulose; PVP-Poly vinyl pyrrolidone

DETERMINATION PERCENT MOISTURE LOSS

The films were accurately weighed and kept in a dessicator containing anhydrous calcium chloride. After 3 days the films were taken out and weighed. The moisture loss was calculated using the formula ,

Percent moisture loss=Initial weight – Final weight / Initial weight X100.

FILM THICKNESS

Thickness of the film was found out at 3 different points by using screw gauge and average thickness was found out.

WEIGHT UNIFORMITY

Each film was weighed individually and average weight of three films was found.

FOLDING ENDURANCE

Folding endurance was determined by repeatedly folding a small strip of film at the same place until it breaks. The number of times the film could be folded at the same place gives the value of folding endurance.

DRUG CONTENT

A film size of 3.2cm diameter was cut in to small pieces and put in a 50ml phosphate buffer solution. It was shaken by mechanical shaker for 3 hours to get a homogenous solution and filtered. The filtrate of 1ml was withdrawn and made up to 10ml. Then it was analyzed for the drug content at 25 1.2nm

***IN VITRO* DRUG RELEASE STUDIES**

A modified dissolution apparatus, consisting of an open ended cylinder was used for assessment of the release of drug from patches. The commercial semi permeable membrane (transparent regenerated cellulose type, permeable to low molecular weight substances) was tied to open ended cylinder. This acted as donor compartment. The entire surface of the membrane was in contact with receptor compartment containing 50ml of phosphate buffer (pH7.4) which was stirred by magnetic stirrer. A transdermal patch was placed in the donor compartment. Samples (1ml aliquots) were pipetted out every hour from the receptor compartment and replaced with the same volume. Each withdrawn sample was diluted suitably and then analyzed spectrophotometrically at 251.2nm.

***EX VIVO* PERMEATION STUDIES**

Transdermal patches were subjected to *ex vivo* permeation studies across rat dorsal skin[4], guinea pig skin[5] and superficial skin taken from the back of pig's ear[6] in order to select the best biological system which has good correlation with *in vitro* release. After removal of epidermal hair, skin was cleaned and any adhering subcutaneous tissue and blood vessels were removed. Each skin was mounted overnight (12h) on receptor phase to remove any water soluble or UV absorbing material. The study was carried out using locally fabricated keshary-chien type of diffusion cell[7]. The diffusion cell consists of following parts; the upper part i.e. the donor compartment contains active ingredient and the carrier adhesive/patch, the bottom part contains the receptor solution, the water jacket for temperature control and the sampling port. The effective permeation area of the diffusion cell and receptor cell volume was 3.2cm and 25ml.The temperature was maintained at 37±2°. The receptor compartment contained 25ml of phosphate buffer pH7.4. Samples (1.0ml) were withdrawn and replaced with the same volume of fresh receptor solution through the sampling port of the diffusion cell at predetermined time intervals till 24h.

EVALUATION OF SKIN IRRITATION POTENTIAL OF POLYMERIC MATRICES

The primary skin irritation studies were done using modified draize test[8].The hair of rabbits were removed by shaving from the dorsal area on both sides 24h before test. One side of the back of each rabbit (untreated skin area) serves as the control for the test. Medicated patch was served on experimental side using adhesive tape and the non medicated patch was adhered on the control side of six rabbits. These patches were covered with occlusive covering to approximate the condition of use. The medicated patches were changed after 24h and the fresh patches were served at the same site. However the patches on the controlled side were not changed. The patches were served on the back for seven days. After removal of patch after a week each of the areas were examined for any sign of erythema or oedema.

TABLE 2: RESULT OF PHYSIOCHEMICAL EVALUATIONOS OF TRANSDERMAL PATCHES OF CELECOXIB

Form. Code	Moisture absorption (%)	Moisture loss (%)	Thickness (mm)	Weight uniformity (mg)	Folding endurance	Drug content (mg)
F1	17.52 ± 0.57	8.58 ±0.32	0.21±0.01	2.414 ±0.02	79±0.57	91.7±0.52
F2	16.24± 0.27	8.21± 0.29	0.26 ± 0.05	0.2388 ±0.02	68±1.14	93.33±0.57
F3	18.2±0.74	14.05± 0.66	0.22± 0.02	0.1902±0.009	70± 0.66	94.37±2.15
F4	26.67±0.7	9.5±0.41	0.21±0.03	0.2109±0.02	81± 0.57	92.33±2.15
F5	18.20±0.55	10.8±0.33	0.20±0.06	0.2081± 0.01	82± 0.57	94.6± 0.74
F6	19.26 ± 0.7	10.69 ± 0.87	0.29 ± 0.05	0.2200 ± 0.03	75± 0.57	93.33±0.57
F7	20.35± 0.36	13.16 ± 0.68	0.21± 0.02	0.1854±0.02	74± 1	84 ± 1
F8	21.07 ± 0.79	5.14 ± 0.16	0.23 ± 0.03	0.1941 ± 0.01	69± 1	84.5±0.72
F9	17.96 ±0.51	12.58 ± 0.79	0.24 ± 0.03	0.204 ± 0.03	84 ± 0.56	93.78±0.7
F10	15.78± 0.59	9.67 ± 0.01	0.24 ± 0.01	0.233± 0.03	78 ± 0.57	90± 0.5

(n=3)

RESULTS AND DISCUSSION

The physico chemical evaluation of the polymeric films showed uniform drug content and minimum batch variation. The thickness of the films varied from 0.20 to 0.29mm. The results also showed uniformity in weight per cm square of area. Folding endurance[9] studies showed the values in the range of 69 to 84 in all batches. This revealed that the films were having capability to withstand the mechanical pressure along with good flexibility.

The percentage moisture absorption[10] of batch F4 was the highest among them. This might be due to high hydrophilicity of HPMC and PVP. The batch F3 showed high percent moisture loss. This could be attributed due to the low moisture retaining capacity. Drug content was varied from90±0.5 (mg) of the film F10 to 90 (mg) of the film F5. On the basis it was found that the drug was dispersed uniformly throughout the film. The physical appearance and effect of ageing indicated that the patches need to be stored in properly sealed airtight packing to protect them from the moisture that may alter their appearance. Thus the properties were found to be within limits and satisfactory. (**Table 2)**

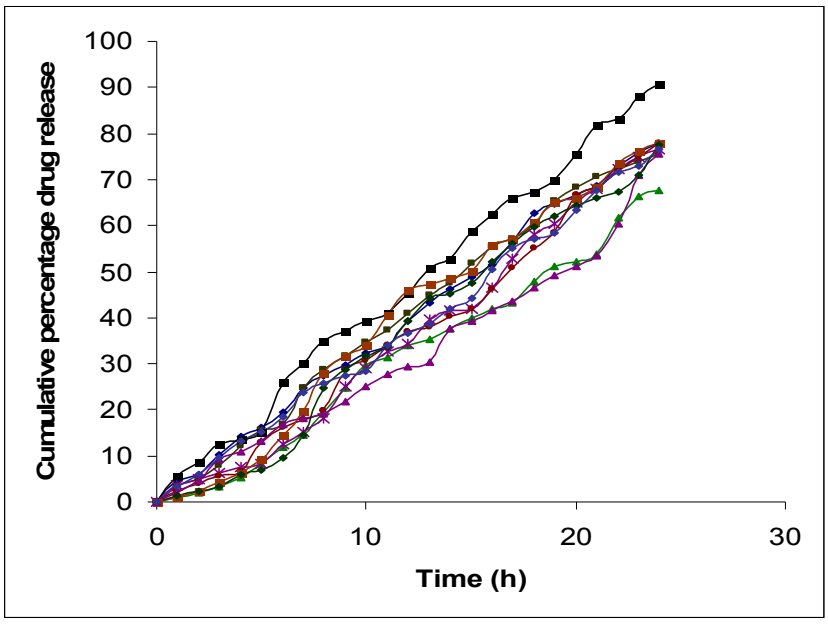

Fig 1: Cumulative percentage of drug release in pH 7.4 buffer for different formulations. Formulation F1(—•—), F2(—▪—), F3 (—▲—), F4 (—■—), F5(—✱—), F6(—•—), F7(—▪—), F8(—▲—), F9(—•—), F10(—•—)

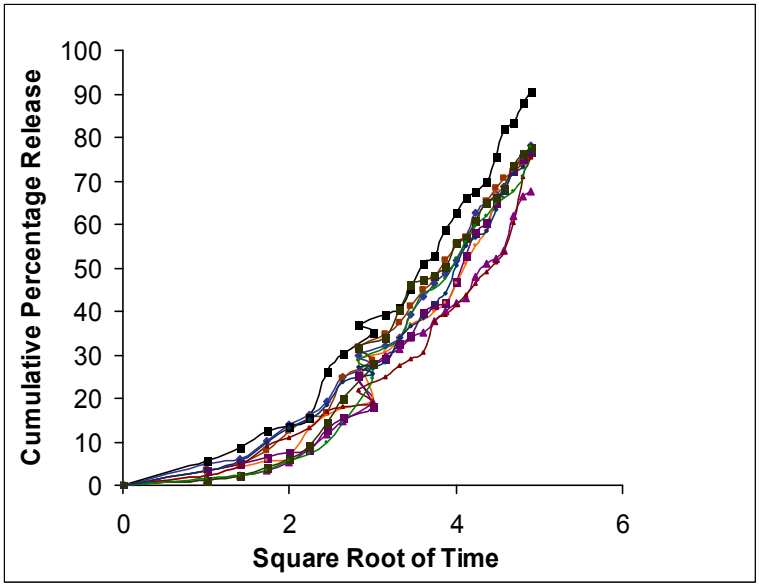

Fig 2: Higuchi's Diffusion plot for different formulations
Formulation F1(—•—), F2(—▪—), F3 (—▲—), F4 (—■—), F5(—●—), F6(—·—), F7(—▲—), F8(—▲—), F9(—·—), F10(—•—)

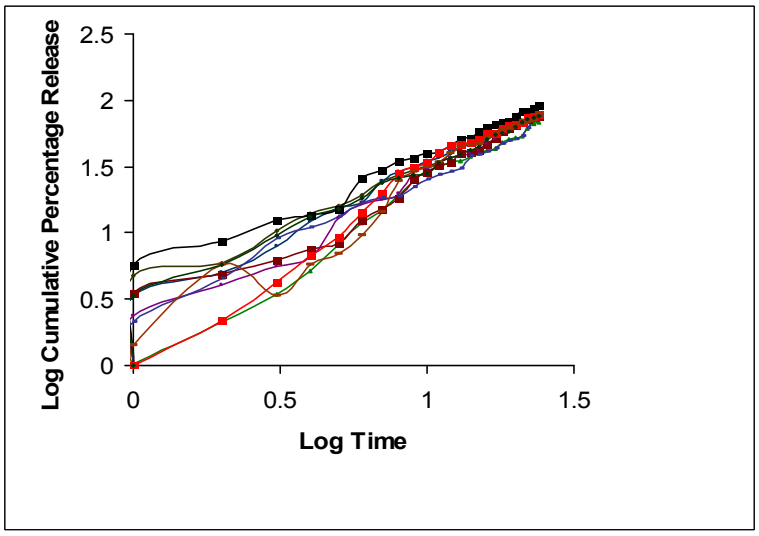

Fig 3: Peppa's plot for different formulations
Formulation F1(—•—), F2(—▪—), F3 (—·—), F4 (—■—), F5(—●—), F6(—▲—), F7(—■—), F8(—▲—), F9(—·—), F10(—•—)

In vitro release studies of various formulations were carried out using pH 7.4 phosphate buffer as the dissolution medium and measuring the drug concentration spectrophotometrically at 251.2nm.. The absorbances of withdrawn samples were measured at 251.2nm. The experiments were done in triplicates, simultaneously blanks were also run and the average values reported. In order to find out the order of release and the mechanism which was influencing the drug release from matrix the *in vitro* dissolution data was subjected to 3 different modes of graphical treatment. They are percentage cumulative drug release versus time, percentage cumulative drug release versus square root of time (Higuchi's Plot), log cumulative percent drug release versus log time (Peppa's Plot). The slope value and the degree of linearity of the above graphical treatments were considered as important statistical parameters to interpret the *in vitro* profile of all formulations.

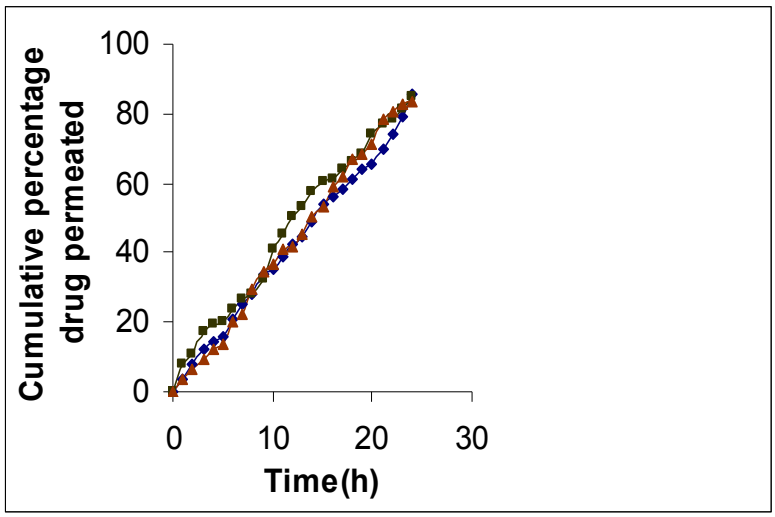

Fig 4*: Ex vivo* permeation studies of selected transdermal patches of celecoxib across rat skin, guinea pig skin, Pig ear skin Permeation studies in pH7.4 buffer of formulation F4 across Rat Skin (—•—), Guinea Pig Skin (—▪—), Pig Ear Skin (—▲—)

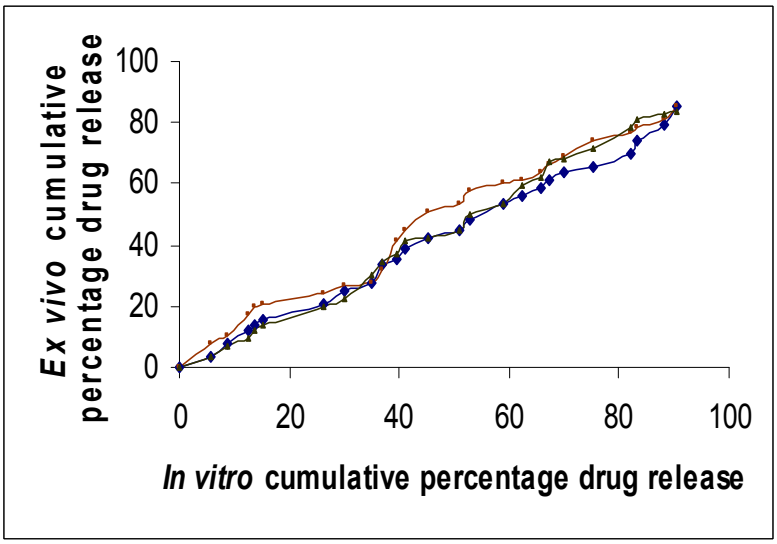

Fig 5: *In vitro* (F4-Selected formulation) - *in vivo* correlation
Correlation between *in vitro* release of F4 and *ex vivo* release of the same across rat skin (—•—), Correlation between *in vitro* release of F4 and *ex vivo* release of the same across guinea Pig Skin (—▪—),Correlation between *in vitro* release of F4 and *ex vivo* release of the same across pig Ear Skin (—▲—)

Order of drug release was confirmed by the *in vitro* drug release plot, (fig1) shows the graphical representation of percentage cumulative drug release versus time. The release was found to follow zero order kinetics from the regression values obtained in comparision with first order plot. Mechanism of drug release whether diffusion, swelling, erosion was confirmed by Higuchi's plot (fig2) shows the graphical representation of cumulative drug release versus square root of time. The Higuchi's plots were found to be linear with regression values of 0.9826, 0.9892, 0.9559, 0.9864, 0.9683, 0.9732, 0.9880, 0.9608, 0.9669, and 0.9538 for the batches from F1 to F10 respectively. It was concluded that the release of drug from the films followed the diffusion controlled mechanism in all the formulation. In order to confirm this fact, Peppa's plot was drawn (fig3) shows the graphical representation of log cumulative percentage drug release versus log time. The slope values of 1.0240, 1.0730, 0.9903, 1.0324, 1.0348, 0.9977, 1.0216, 1.0428, 1.0082, 0.9870 for the batches from F1 to F10 respectively, which confirmed that the diffusion

mechanism involved in the drug release was of non-fickian diffusion type[11].

The release of Celecoxib in 24h was found to be 67.71 to 90.67% for the formulation from F1 to F10 respectively. Amongst all the formulations, formulation F4 showed the good release pattern as compared to others. On the basis of release pattern, F4 was selected for *ex vivo* study. Drug diffusion was found to be 85.39%, 85.19% and 83.80 % respectively for rat, guinea pig and pig ear skin (fig 4). This variation could be attributed to the fat content and thickness of membranes used. As earlier studies indicate that the human skin has the best correlation with rat skin, the results were analyzed in this point of view. As the rat skin has shown good correlation with *in vitro* release of F4 (fig 5**),** this was considered for further studies. The primary skin irritation studies of F4 showed that F4 does not cause any irritation after 7 days of application. *In vivo* studies need to be designed and executed to substantiate further *in vitro in vivo* correlation.

CONCLUSION

In the present study, hydrophobic drug celecoxib was successfully incorporated in to transdermal patches composed of different polymers with desired qualities.

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REFERENCES

1. Davies NM, Mc Lachan AJ, Day RO, William KM, Clinical Pharmacokinetics and Pharmacodynamics of Celecoxib: A selective Cyclo oxygenase 2 inhibitors. **Clin Pharmacokinetic** 2000;38: 225-42
2. Saha RN, Sajeev C, Girish B, Punnarao Studies on design and evaluation of controlled release polymeric discs for ocular delivery of flurbiprofen and celecoxib. **Indian J Pharm Sci** 2002; 325-326
3. Murthy TK, Reddy MN, Sankar DG, UV spectrophhotometric methods for the determination of celecoxib and tizanidine hydrochloride. **Indian J Pharm Sci 2001;521-523**
4. Hiroven rytting,J. **Pharmaceutical Research** 1991; 933
5. Ramesh Panchagunla, Transdermal Delivery of drug. **Indian Journal of Clinical Pharmacology** 1997; 29, 140.
6. Kaidi Zhao, Jagadish Singh, **J Control Release** 1999; 62, 359-366.
7. Keshary pr, chein Yw. Mechanisms of transdermal controlled nitroglycerin administration (I). Development of finite dosing skin permeation. **Drug develop Ind Pharm** 1984; 10:883-913.
8. Draize JH, Woodward GS, Calvary HO Method for the study of irritation and toxicity of substances applied topically to the skin and mucus membrane. **J pharmacol exp Ther** 1994; 82: 377-90.
9. Koteshwar KB, Udupa N, Vasantha kumar, Design and evaluation of captopril transdermal preparation. **Indian Drugs** 1992; 29, 680-685.
10. Sachan A, Jain DK, Trivedi P, Simultaneous determination of captopril and hydro chlorthiazide in two compartment tablets by UV spetrophotometry. **Indian J Pharm Sci,** 1997; 59 (1):29
11. Haririan, Ghaffari A., Mohammed-pour, Formulaton of controlled release matrix tablets of Iso Sarbide Dinitrite. **Indian J Pharm Sci** 2001;63(1):28.

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