PREPARATION AND IN-VITRO IN-VIVO EVALUATION OF SUSTAINED RELEASE MATRIX DICLOFENAC SODIUM TABLETS USING PVP-K90 AND NATURAL GUMS

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ABSTRACT

Conventional dosage form is nowadays mostly replaced by sustained release formulation in order to increase drug efficacy and patient compliance. The sustained release properties of the PVP K90 alone and in combination with guar gum, xanthan gum and gum tragacanth were evaluated using diclofenac sodium (100 mg/tablet) as a model drug. Tablets were processed using wet granulation method and evaluated for sustained drug release properties. The drug release from the formulations was studied in relationship with Commercially available Diclofenac Sodium SR, used as a reference tablets and results were expressed as similarity (*f*1) and differential factor (*f*2). The tablets prepared using PVP K90 160 mg/tablet sustained the release of diclofenac sodium for 12 hours. Formulations where the PVP K90 was partially replaced with different gums also sustained the release of drug for 12 hours. The release of the drug from these formulations mainly followed Higuchi model and super case-II and Non-Fickian diffusion. The in-vivo drug release was studied in healthy human volunteers using non-blinded cross over, two period design using Diclofenac Sodium SR Tablets as a reference drug. The relative bioavailability of the formulation containing PVP K90 and gum tragacanth was 0.91. The studies showed that the use of the PVP K90 in combination with gum tragacanth both in-vitro and in-vivo sustained the release of the drug.

Keywords: Sustained release, PVP K90, Guar gum, Xanthan gum, Gum Tragacanth.

INTRODUCTION

Naturally occurring, synthetic and semisynthetic polymers are used in pharmaceuticals and cosmetic preparations for several decades. It includes hydrophilic polymers, hydrophobic polymers or polymers having both the properties. The hydrogel forming polymers control the release of the drug by swelling and cross linking and release the entrapped drug into aqueous medium (Chien, 1992; Kumar and Neeraj, 2001). The formulation of the hydrophilic sustained release matrix tablets is simple and cost-effective and reduces the risk of toxicity due to the dumping of the dose (Gao and Meury, 2000; Gohel and Amin, 1998). Penetration of the water, swell up the polymer and dissolve the drug that diffuse through the gels, also part of the drug is released through polymer erosion (Sung *et al*., 1996). The rational composition of the polymer and modulation of polymer in the matrix system can control the plasma drug profile over the period of time (Reza *et al*., 2002). The amount of polymer, polymer viscosity and the addition of various excipients to the matrix tablets can modify the release of the drug from the dosage form, In addition, the method of preparation and technological parameters can influence the release of drug from the polymer matrices (Vazquez *et al*., 1992).

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Natural polymers like cellulose, xanthan gum, locust bean gum, gaur gum and chemically modified gums have been studied in hydrophilic matrix tablets for controlled drug delivery (Nishi *et al*., 2007; Díez-Peña *et al*., 2004; Aguzzi *et al*., 2002; Krishnaiah *et al*., 2002; Toti and Aminabhavi, 2004). These natural polymers are usually cost effective, nontoxic and easily available. Guar gum in pharmaceuticals is used as disintegrant, binder (Wassel *et al*., 1989; Rowe *et al*., 2003; Baweja and Misra, 1997) and as a hydrophilic matrix for sustaining drug release (Berner-Strzelczyk *et al*., 2006; Varshosaz *et al*., 2006; Khullar *et al*., 1998; Misra and Baweja, 1997). Xanthan gum is an another industrially important exocellular heteropolysaccharide natural gum, used as thickening agent (Castro *et al*., 2003) and also has been used as hydrophilic sustained release matrix material for different drugs (Lu *et al*., 1991; Dhopeshwarkar *et al*., 1994; Cooper and Gunn, 1986). Tragacanth is a naturally occurring dried gum comprised of bassorin (60-70%), the water insoluble portion and tragacanthin, water soluble portion (30-40%). When water permeates, the tragacanthin dissolve forming colloidal hydrosol and bassorin swell up to form a gel like material and by this mechanism the release of the drug from the matrix system is controlled. The present work aimed to study the sustained release properties of the PVP K90 alone and with the combination of the natural gums using diclofenac sodium as a model drug.

MATERIAL AND METHODS

Materials

Diclofenac sodium (Ningbo Smart Pharmaceutical Co. Ltd, China), lactose (The Lactose Newzeland Company, Newzeland), polyvinylpyrrolidone (PVP-K90) (BASF Ltd., UK), guar gum, xanthan gum, (Medicraft pharmaceuticlas. Pvt. Ltd. Peshawar, Pakistan), magnesium stearate, talc, sodium bicarbonate (BDH, England), di-Sodium hydrogen phosphate, Sodium citrate (Merck, Germany).

Instrumentation

Oscillating granulator (F.D & C Karachi, Pakistan), ZP19 Rotary Tablet Press (STC, Shanghi, China), tablet hardness tester (model THB, Erweka, Germany), Dissolution test Apparatus (Erweka, Germany), Friabilator (Erweka, Germany), UV/Visible spectrophotometer (Hitachi, Japan).

Methods

Preparation of Tablets

Tablet formulations shown in table 1, were prepared using wet granulation method, simply diclofenac sodium, PVP-K90 and lactose were mixed in conventional mixer. Then sufficient volume of ethanol, used as wetting agent, was added and mixed thoroughly and passed through mesh No. 16 and dried at 40˚C for 12hours. The dried granules were passed through mesh NO. 22, the lubricant and glidants were added and mixed thoroughly. The physical characteristics of the granules were evaluated. The weight of the tablets was calculated on the basis of percent drug contents and compressed into tablets using beveled edge punches (11.8 mm) on ZP 19 rotary tablet press and evaluated using different tests.

Evaluation of Granules

Various physical properties of the granules like angle of repose, loose and tapped bulk densities (Shah *et al*., 1997) and compressibility index (Aulton, 1988) were determined.

Drug contents in granules and tablets were determined according B.P (Pharmacopoeia B, 2004).

Physical characterization of matrix tablets

The weight variation and friability of the tablets was determined according to B.P. (Pharmacopoeia B, 2004), the thickness and the hardness of tablets (n =20) was measured using Pharma test hardness tester.

Dissolution Profile

Drug release from the tablets (n=6) from each batch of formulations were evaluated using USP dissolution apparatus I, adjusted at 50 rpm. Water (900 ml) adjusted at 37°C ± 1.0 was used as medium. Samples were collected periodically and analyzed for the drug contents.

The Difference Factor (f1) and Similarity Factor (f 2)

The dissolution data for various formulations was evaluated for the difference factor (f1) (Mutalik and Hiremath, 2000) and similarity factor (f2) (Emami, 2006) using equation I and II, respectively. .

$$f1 = \left\{\left[\sum_{t=1}^{n}\left|R_t - T_t\right|\right] \Big/ \left[\sum_{t=1}^{n} R_t\right]\right\} \times 100 \qquad \text{I}$$

Where, n is the number of time points, Rt is the dissolution value of the reference batch at time t, and Tt is the dissolution value of the test batch at time t. generally f1 values varies from 0 to 15 (Mutalik and Hiremath, 2000).

Table 1: Composition of Diclofenac sodium tablets (100 mg of active ingredients)

S. No.	Formula	PVP-K90 (mg)	Guar gum (mg)	Xanthan gum (mg)	Gum Tragacanth (mg)	Lactose (mg)	Buffer (mg)
1	DFP1	80	-	-	-	210	-
2	DFP2	100	-	-	-	190	-
3	DFP3	120	-	-	-	170	-
4	DFP4	140	-	-	-	150	-
5	DFP5	160	-		-	130	-
6	DFP6	160	-	-	-	120	10 Sodium bicarbonate
7	DFP7	160	-	-	-	120	10 Sodium citrate
8	P_2G_2	80	80		-	130	-
9	P_2X_2	80	-	80	-	130	-
10	P_2T_2	80			80	130	-
11	P_2GX	80	40	40	-	130	-
12	P_2GT	80	40		40	130	-
13	P_2XT	80	-	40	40	130	-

DF = Diclofenac sodium, P= Polyvinylpyrrolidone (PVP-K90), PG = PVP-K90+ guar gum, P_2X_2 = PVP-K90 + xanthan gum, P_2T_2 =PVP-K90 + gum tragacanth, P_2GX = PVP-K90 + guar gum + xanthan gum, P_2GT= PVP-K90 + guar gum + gum tragacanth, P_2XT =PVP-K90 +xanthan gum+ gum tragcanth

$$f2 = 50log\left\{\left[1 + (1/m)\sum_{j=1}^{m} w_j |R_j - T_j|^2\right]^{-0.5} \times 100\right\} \quad \text{II}$$

If the value of f1 is less than 15 and value of f2 is between 50 and 100, then formulations under studies are considered as similar to the reference drug (Costa, 2001).

Determination of the release rate of Diclofenac Sodium

The cumulative drug release (%) as a function of time (Zero Order), log of the cumulative drug release (%) as a function of Time (First Order), cumulative drug release (%) as a function of square root of time (Higuchi Model) and cube root of remaining drug vs time (Hixon-Crowell) plots were constructed to understand the drug release mechanism.

To understand the mechanism from the polymeric system Korsmeyer's-Peppas model was applied, the value of "n" less than 0.45 shows the Fickian Diffusion, between 0.45 and 0.89 indicates the non-Fickian or anomalous diffusion, 0.89 indicates the case-II transport and above 0.89 shows super case diffusion. .

Pharmacokinetics studies

In vivo Evaluation of PVP-K90 matrix tablets

In vivo studies were performed following standard protocols in accordance with all applicable regulations according to the Helsinki declaration (Williams, 2008) in 6 healthy human male volunteers of mean weight 61.2 ± 11.2 Kg (ranged between 55-75 kg) and age 23.8 ± 4.1 years (22 to 26 years). The study was approved from the Ethical Committee of the Health Department of Government of KPK (Pakistan). The protocol of the studies and side effects and other pharmacological properties of the drugs were explained to volunteers. The physical examination and biochemical screening (blood glucose, alkaline phosphatase, liver function test, serum creatinine etc.) and haematology of all the volunteers were normal. The volunteers were non-smokers, non-alcohol user and were not using any type of medicine. All the participants were asked not to take any food overnight, a day before the experiment.

The study was conducted using non-blinded, single dose, two way cross-over design with a wash out period of one week. The test or reference medicines were administered to the volunteers at 7:30 am with full glass of water. The breakfast and lunch was served following 3 and 5 hour of the drug administration. Blood samples following the oral administration of the drugs were collected using porcelain syringe (≈ 5 ml) at 0 (before drug administration) , 1, 2, 4, 6, 8, 12 and 16 and 24 h hours in glass tubes with screw caps post oral administration of the drug. The serum was collected and transferred into glass tube (Ca ≈ 5 ml) with screw cap and stored at -70°C until analysis.

DATA ANALYSIS

Serum samples were analyzed and plotted as a function of time for each volunteer both for test and reference formulations. Various pharmacokinetics parameters were then calculated. The C_{max}, T_{max} were directly obtained from the plot and $[AUC]_0^t$ was calculated by Trapezoidal method. The PK-Solution software was used for the calculation of various PK parameters for both drug and for each volunteer and the data is then presented as mean (± SD) for all parameters.

HPLC analysis of drug samples

The diclofenac sodium in serum samples was analysed using Perkin Elmer HPLC (series 200) equipped with UV-Visible detector (Perkin Elmer Series 200). The analytes were separated on Kromasil KR100 – 10 C_{18} (ODS; 5 C-18 µm; 250 x 4.6 mm) column and measured at 245 nm. The analytical column was protected with the guard column (Guard-Pak filled with a µ Bondapak C-18 cartridge, Merk, Germany).

Diclofenac Sodium was separated using phosphoric acid (0.2M) and methanol (80:20) as mobile phase and pumped at 2 ml^{-1} and monitored at 245 nm. Prior to analysis serum samples were thawed at room temperature and acetaminophen (20 ng), used an internal standard, was added and vortexed for 1 min. Then, acetonitrile (400 µl) and phosphoric acid (100 µl; 0.25 M) were added, vortexed for further 1 minute and centrifuged at 10,000 g for 10 minutes. The supernatant was collected and evaporated to dryness under stream of nitrogen. The residue was redissolved in mobile phase (100 µl) and 20 µl was injected into HPLC for analysis.

RESULTS

Physical properties of granules and tablets prepared using PVP-K90 alone and admixed with natural gums

Physical characteristics of the granules and tablets depicted in table 2 were found satisfactory. Generally no significant changes in the physical properties of the granules or tablets were observed and were not possible to correlate the polymer/gums ratio with the physical characteristics of granule or tablets. However, a typical increase in hardness and decrease in friability of the tablets was observed in data.

Angle of repose and compressibility index (%) of the granules ranged from the 22.19 to 24.13 and 10.03 to 14.5, respectively. The LBD and TBD values ranged from 0.287 to 0.428 and 0.332 to 0.486, respectively, all these parameters were within the specified limits. The drug content in the granules of all formulations was above 97.98% and was uniform in all formulations. Density of granules, porosity, and hardness are often interrelated properties.

The thickness of the tablets ranged from 4.18 to 4.42 mm. The average weight deviation (%) of 20 tablets for all formulations was less than ± 5%. Drug content was found to be uniform among different batches of the tablets and ranged from 97.85% to 99.62%. All the formulations complied with pharmacopoeal specifications for weight variation, drug content, hardness and friability.

Release of the drug from matrix tablets

The dissolution profile of all the formulations is shown in fig. 1**,** tablets DFP1, DFP2, DFP3, DFP4 and DFP5 released 32.58%, 28.14%,14.78%, 10.21%, and 8.14% of diclofenac sodium, respectively in 1st hours. The formulation DFP5 showed better sustaining properties and retarded the release of the drug up to 12 hours. The formulation DFP6 and DFP7 containing buffers released 16.56%, 22.41% of diclofenac sodium, respectively at the end of 2 hours and 96.86%, 90.78%, at the end of 10 hours, respectively.

The dissolution profile of the matrix tablets prepared using admixed polymers in the phosphate buffer solution of pH 6.8 are shown in fig. 2. The formulations P_4, P_2G_2, P_2X_2, and P_2T_2 released 28.62%, 26.32%, 24.62% 25.42% of diclofenac sodium, respectively in first 2 hours and 98.18%, 93.42%, 88.46% and 91.88% of drug at the end of 12 hours, respectively.

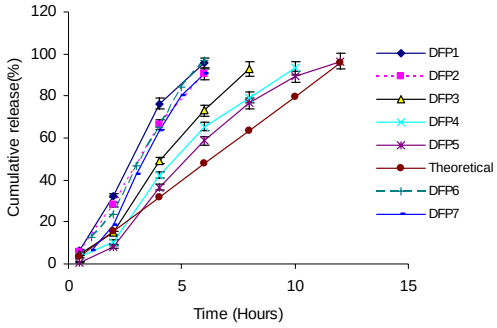

Fig. 1: Cumulative percentage (mean ± SD) of Diclofenac sodium released from SR matrix tablets using different amount of PVP-K90 (n = 3)

Table 2: Physical Properties of the granules and Tablets prepared using PVP K90 alone and in combination with various gums

Formula-tion	Granules					Tablets			
	Angle of repose	Loose bulk density (LBD) (g/ml)	Taped bulk density (TBD) (g/ml)	Compress ibility Index (%)	Drug content %	Thickness (mm)	Hardness (N)	Friability (%)	Drug content (%)
DFP1	22.63 ± 0.03	0.289 ± 0.04	0.335 ± 0.03	13.73± 0.02	98.56 ± 0.05	4.42 ± 0.02	80 ± 2.4	0.75± 0.03	98.60± 0.05
DFP2	22.19 ± 0.02	0.287 ± 0.02	0.332 ± 0.05	13.55± 0.04	99.34 ± 0.03	4.39 ± 0.04	90± 1.9	0.69± 0.04	99.10± 0.02
DFP3	23.93 ± 0.02	0.302 ± 0.02	0.353 ± 0.04	14.44± 0.03	99.01 ± 0.02	4.35 ± 0.04	98± 2.5	0.72± 0.04	98.92± 0.05
DFP4	22.76 ± 0.03	0.301 ± 0.04	0.352 ± 0.03	14.45± 0.02	97.98 ± 0.03	4.35 ± 03	103± 2.3	0.54± 0.02	98.57± 0.04
DFP5	24.13 ± 0.04	0.307 ± 0.03	0.356 ± 0.03	13.76± 0.04	98.89 ± 0,04	4.28 ± 0.04	115± 2.4	0.52± 0.02	97.85± 0.05
DFP6	23.68 ± 0.03	0.306 ± 0.03	0.354 ± 0.05	13.59± 0.04	98.87 ± 0.03	4.37 ± 0.04	113± 1.9	0.58± 0.04	98.48± 0.04
DFP7	23.92 ± 0.03	0.304 ± 0.03	0.352 ± 0.05	13.64± 0.04	98.91 ± 0.02	4.39 ± 0.02	114 ± 2.1	0.62± 0.03	98.52± 0.04
P2G2	26.46 ± 0.02	0.397 ± 0.02	0.454 ± 0.05	12.55 ± 0.02	99.32 ± 0.02	4.22 ± 0.03	88 ± 2.4	0.38 ± 0.05	99.14± 0.02
P2X2	23.24 ± 0.02	0.412 ± 0.02	0.458 ± 0.04	10.03 ± 0.03	98.86 ± 0.04	4.18 ± 0.03	98 ± 2.3	0.46 ± 0.04	99.34± 0.05
P2T2	25.56 ± 0.03	0.425 ± 0.04	0.478 ± 0.03	11.08 ± 0.02	99.92 ± 0.04	4.29 ± 0.02	89 ± 1.9	0.37 ± 0.04	97.94± 0,04
P2GX	24.48 ± 0.04	0.417 ± 0.03	0.472 ± 0.03	11.65 ± 0.04	98.72 ± 0.03	4.18 ± 0.04	88 ± 2.4	0.34 ± 0.03	98.35± 0.05
P2GT	23.68 ± 0.03	0.402 ± 0.03	0.464 ± 0.02	14.71 ± 0.04	98.62 ± 0.02	4.22 ± 0.02	83 ± 1.9	0.29 ± 0.04	99.58± 0.04
P2XT	24.24 ± 0.03	0.428 ± 0.02	0.486 ± 0.04	11.93 ± 0.02	99.28 ± 0.02	4.25 ± 0.04	91 ± 2.1	0.38 ± 0.03	99.12± 0.04

All values represent mean ± SD (n = 3)

Table 3: *In vitro* drug release kinetics of Matrix tablets formulations containing PVP-K90 and PVP K90 admixed with natural gums

Formulation	Zero Order	First order	Higuchi	Korsmeyer			Formulation
	R^2	R^2	R^2	R^2	n	k	
DFP1	0.9897	0.8475	0.9804	0.9933	1.13	1.16	Super caseII
DFP2	0.9498	0.9069	0.9560	0.9973	1.15	1.10	Super caseII
DFP3	0.9762	0.8652	0.9560	0.9822	1.13	0.952	Super caseII
DFP4	0.9923	0.8889	0.9740	0.9698	1.17	0.839	Super caseII
DFP5	0.9766	0.7628	0.9721	0.9798	1.54	0.467	Super caseII
DFP6	0.9721	0.8818	0.9724	0.9764	0.707	1.26	Non-Fickian
DFP7	0.9873	0.9147	0.9873	0.9929	0.824	1.05	Non-Fickian
P_2G_2	0.9855	0.9920	0.9970	0.9920	0.711	1.22	Non-Fickian
P_2X_2	0.9929	0.9970	1.00	0.9970	0.712	1.19	Non-Fickian
P_2T_2	0.9901	0.9950	0.9990	0.9950	0.717	1.21	Non-Fickian
P_2GX	0.9885	0.9930	0.9990	0.9930	0.725	1.19	Non-Fickian
P_2GT	0.9846	0.9930	0.9970	0.9930	0.693	1.24	Non-Fickian
P_2XT	0.9877	0.9920	0.9990	0.9920	0.731	1.17	Non-Fickian

Table 4: Similarity (*f*1) and Difference factors (*f*2) of various formulations, Diclofenac Sodium SR is used as Reference standard.

	DFP1	DFP5	DFP7	DFP8	P2G2	P2X2	P2T2	PTGX	P2GT	P2XT
f1	-6.27	3.311	11.96	19.94	4.21	-3.85	0.29	-2.75	5.46	-4.54
f2	65.23	61.72	54.72	45.96	62.64	60.82	64.58	61.92	59.09	58.29

The formulation P_2X_2 and P_2T_2 effectively retarded the release of the drug compared with the other formulations. Using the PVP K90 with the combination of two gums i.e. formulations P_2GX, P_2GT, and P_2XT released 24.26%, 26.84% and 23.22% of diclofenac sodium, respectively at the end of the first 2 hours and 89.64%, 92.04% and 86.26% at the end of 12 hours, respectively.

Table 5: Non-Compartmental pharmacokinetics parameters of formulation P_2T_2 and Diclofenac Sodium SR (reference standard), following Oral administration of the drug in healthy Human Volunteers.

Parameter	P_2T_2	Diclofenac Sodium SR (reference standard)
C_{max} (µg/ml)	0.46	0.51
T_{max} (h)	4.00	4.00
AUC $_{0\text{-}24}$ (µg/h/ml)	3.13	3.40
AUC $_{0\text{-}\infty}$ (µg/h/ml)	3.27	3.61
t ½ (h)	6.91	6.83
AUMC area (µg-h*h/ml)	20.97	24.11
MRT (area) (h)	6.50	6.63

DISCUSSION

Initially, matrix tablets were prepared using PVP-K90 (DFP5) alone as the retarding material. In order to obtain the matrix tablets with improved sustained release properties and cost effective formulation the PVP K90 was partially replaced with natural gums, used as sustaining material. The physical properties of the granules and tablets (P_2G_2), containing PVP-K90, and guar gum, were within the limits of the official specifications. The drug released was extended for 12 hours in phosphate buffer of pH 6.8. Similarly, the formulations P_2X_2 and P_2T_2, containing PVP-K90 with xanthan gum and gum tragacanth, respectively extended the release up to 12 hours (fig. 2). The release of the drug from the formulation PVP K90 alone (DP5) was relatively faster compared with the formulations containing PVP K90 in combination with the gums. The formulations containing PVP K90 and more than one gums i.e. P_2GX, P_2GT and P_2XT, the formulations P_2XT slower the release of the drug from more than 12 hours, while the release of the drug from the formulation P_2GT was relatively faster.

The release of the diclofenac sodium from formulation DFP5 is closest to the theoretical release profile values (Sheu *et al*., 1992) that released 4.07 mg in first hour and 36.62 mg in 4 hours followed by approximately 17 mg an average after each 2 hours. In the first 2 hours of the dissolution studies, the release of the drug was slow; it may be due to the poor solubility of diclofenac sodium in acidic medium and it dissolves readily in intestinal fluid and water (Vlachou *et al*., 2000). The low solubility of diclofenac sodium in acidic medium may limits the initial release of surface drugs as well as the formation of channels within the matrix. Consequently, the overall

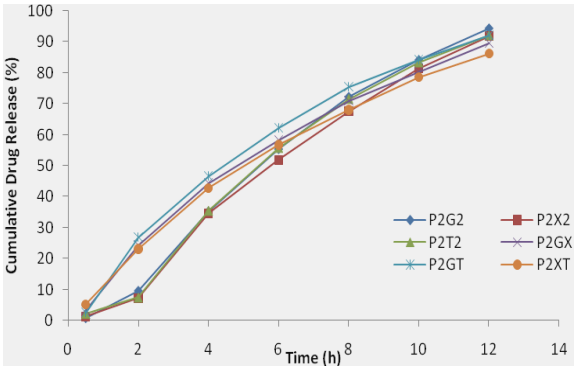

Fig. 2: Cumulative percentage (mean ± SD) of Diclofenac sodium released from SR matrix tablets using PVP-K90 and gums (n = 3).

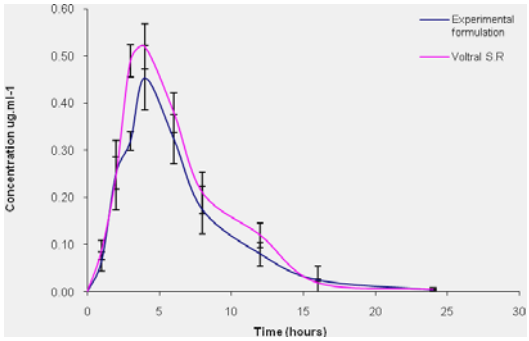

Fig. 3: Plasma Concentration Time Curve of Diclofenac sodium SR (reference standard) vs formulation P_2T_2 n healthy human volunteers

release of diclofenac sodium is decreased. The water-soluble material such as lactose can stimulate the water penetration into the inner parts of the matrix, thus resulting increase in the drug release from matrix (Sheu *et al*., 1992; Vlachou *et al*., 2000). Due to the poor solubility of diclofenac sodium lactose was included in the formulation as diluents and also to help in the release of the drug matrix tablets. The addition of buffers (sodium bicarbonate or sodium citrate) increased the release rate of diclofenac sodium from PVP-K90 matrix tablets. The drug release rate of the drug was higher from the formulation DFP6 containing sodium bicarbonate as compared to the formulation DFP7.

However, the combination of the xanthan gum with PVP K90, the formulation P_2X_2 retarded the release of drug for longer time than other combinations. Incorporation of the natural gums into the PVP-K90 retarded the release rate of diclofenac sodium from the matrix tablets.

The hydration of the polymer produces highly viscose gel that plays an important role in release of drug, especially at the beginning of the release profile. Therefore, rapid hydration followed by the formation of gel is the key property of an excipient to be used in sustained release matrix formulations. The matrix tablets prepared in the present studies when exposed to dissolution medium hydrated and formed the gel around the matrix, as a result the dissolved drug diffuse through the gel at rate determined by the amount of polymer/gum drug ratio in the formulation.

All the formulations, showed a biphasic release profile. The results showed that there was relatively faster drug release for about 2 hours, followed by a slower release from 3 to 12 hours. It may be due to the drug present in the superficial layer that is in direct contact with dissolution medium from the peripheral side of the tablet that quickly dissolve during the early time and slowest release was observed after 4 hours. The drug present on the surface of the matrix tablet might have resulted in the initial relatively fast release of the drug from the formulation.

The drug release data of the formulations was fitted in zero order, first-order, Higuchi's, and Korsmeyer's models to understand the drug release mechanism. The release rate kinetic data for all the models was evaluated using regression coefficient analysis (Nokhodchi *et al*., 2002) are shown in table 3. Drug release from the hydrophilic matrix tablet into the fluid usually involves the diffusion mechanism that can be explained by the Higuchi model (Sankar *et al*., 2001). The in-vitro release profiles of drug from all these formulations showed good linearity (r^2 = 0.9560 to 0.9873). However, these models were not sufficient to explain the drug release phenomena due to combination of swelling and erosion of matrix. Therefore, the dissolution data was also fitted into Korsmeyer model, which is often used to describe the drug release behavior from polymeric systems. The formulations showed higher linearity (r^2=0.9698 to 0.9973). The formulations DFP1, DFP2, DFP3, DFP4 and DFP5 followed super case II type of release, which refers to the erosion of the polymeric chain and anomalous transport (Higuchi, 1963). The water soluble drug usually follow the anomalous release and water insoluble drugs shows the case-II or zero order drug release mechanism that indicates the drug release is controlled by both diffusion and erosion mechanism. In case of drugs with low solubility, erosion dominates the drug release (Peppas, 1985). The formulations DFP6 and DFP7 followed anomalous transport (Non-Fickian), The presence of sodium bicarbonate and sodium citrate in the formulations, which has improved the solubility of diclofenac sodium.

The drug release data of PVP K-90 admixed with natural gums sustained release tablets was fitted in zero-order (cumulative amount of drug released vs. time), first-order (log cumulative percentage of drug remaining vs. time),

Highuchi's (cumulative percentage of drug released vs. square root of time) model and Korsmeyer (log cumulative percentage of drug released vs. log time) equations.

The drug release data was best fitted into Higuchi model (R^2 =0.9930) and when subjected to Korsmeyer equation it showed super case II release (n = 1.27), the results are depicted in table 3. The in-vitro release profiles of diclofenac sodium from all the formulations containing PVP K-90 in combination with different proportions of admixed natural gums could be best expressed by Higuchi's model. To confirm the diffusion mechanism, the data were also fitted into Korsmeyer model that showed good linearity (R^2: 0.992 to 0.997), with slope (n) values ranging from 0.693 to 0.731, which are greater than 0.45 and less than 0.89, indicate a coupling of diffusion and erosion mechanism so called anomalous diffusion. The release of the drug from the admixed polymer matrix tablets was by dual mechanism i.e. diffusion and erosion.

The present studies showed that PVP-K90, xanthan and tragacanth possess higher gelling ability have the potential for sustaining and/or controlling the release of the drug for longer period. The polymer with higher gel strength and viscosity was incorporated into the core, the release of the drug was more prolonged, the formulations, P_2X_2, P_2T_2 and P_2XT released the drug slowly compared with other formulations.

The difference factor (*f*1) and similarity factor (*f* 2) for various formulations that sustained the release of the drug were studied using Votral SR as a reference drug. All of the formulations containing natural gums showed good similarity (*f2*) and difference (*f1*) with the Diclofenac Sodium SR (reference standard) tablets. However formulations DFP1, DFP5 and DFP 7, containing PVP only, passed the difference and similarity tests while f1 and f2 values for DFP8 not in the acceptance range as shown in table 4.

The results of in-vitro drug release studies in simulated GI fluid (with out pepsin) and simulated GI fluids fluid (with out pancreatin) showed that matrix tablet containing 40% wt/wt of polyvinylpyrrolidone (PVP-K90) was able to control the release of diclofenac sodium. The *in vivo* pharmacokinetic evaluation of PVP-K90 matrix tablets in human volunteers showed a slow and prolonged release of diclofenac sodium indicating the potential for clinical studies.

The natural gums used in combination with the PVP K90 showed little deviation from the theoretical release pattern throughout the dissolution studies. From a commercial point of view, locally available gums are more economical than the synthetic or semi-synthetic polymers. The present studies indicates that the admixed polymers are the most successful and cost-effective formulations among the matrix tablets.

In-vivo drug delivery

The mean (± SD) plasma drug concentration as a function of time curve of diclofenac sodium following oral administration of P_2T_2 tablets and Diclofenac Sodium SR (reference standard), used as a reference drug, (dose 100 mg) is shown in fig. 3. The non-compartmental parameters of both P_2T_2 formulation and reference drugs are shown in table 5. The relative bioavailability calculated using equation III of the formulation P2T2 was 0.911. This indicates the in-vivo release of the diclofenac sodium from the tablet formulation P2T2 is good compared with the Diclofenac SodiumSR (reference standard).

$$\text{Relative Bioavailability} = \frac{[AUC]_0^{\infty}\ (P_2T_2)}{[AUC]_0^{\infty}\ \text{Voltral SR}} \qquad \text{III}$$

The C_{max}, T_{max}, $[AUC]_{0\text{-}24}$ and MRT values of the Volteral SR tablets are close to other studies (Tahara *et al*., 1996). Various other pharmacokinetics parameters of tablets under evaluation were very close to the Diclofenac SodiumSR tablets, used as a reference drug. The lower C_{max} and prolonged T_{max}, of diclofenac sodium in human volunteers indicated that the drug release from the PVP-K90-gum tragacanth matrix tablets was slow thereby providing a prolonged and controlled *in vivo* drug delivery (Su *et al*., 2003). These *in vivo* absorption characteristics are in confirmation with the observed in vitro drug release rate of the drug from the PVP-K90 – gum Tragacanth matrix tablets.

CONCLUSION

In conclusion PVP K90 and gum at the drug: polymer ratio 1:3 sustained the release of the drug for about 12 hours. The addition of the buffers increase the initial release of the diclofenac from the dosage form however, drug release was sustained for about 10 hours. The combination of PVP K90 and natural gum also sustained the release of the diclofenac sodium for about 12 h however, the best similarity and differential factors were obtained with the combination of PVP K90 and gum tragacanth (P_2T_2). The in-vivo pharmacokinetics parameter in healthy human volunteer in comparison with Diclofenac SodiumSR showed bioavailability from this combination. This combination PVP K90 and natural gums can be effectively used for the formulation of sustained release matrix tablets.

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