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THE FORMULATION OF DICLOFENAC SODIUM HYDROGEL TABLETS

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Abstract
Sustained release (SR) diclofenac sodium tablets (100 mg) containing hydroxypropylmethylcellulose (HPMC) and sodium carboxymethylcelluose (NaCMC) as release control hydrogel matrix agents were prepared and evaluated in the study. The dissolution profiles of the tablets were compared to those of Geigy's Voltarol Retard tablets 100 mg using the USP dissolution apparatus paddle method. The SR hydrogel tablets prepared in the study exhibited sustained release characteristics but there was a marked difference in the dissolution profiles when compared to Voltarol Retard tablets. The dissolution data fitted to Higuchi and Hixson-Crowell equations indicating the existence of diffusion mechanism controlling diclofenac release from the tablets

Keywords: Sustained release, diclofenac sodium hydrogel tablets, Voltarol retard tablets, film coating, dissolution profiles

INTRODUCTION

Several physical methods are used to retard oral medications intended for systemic circulation and controlled release. Hui *et al.* (1978) have provided a comprehensive list of the techniques which include: encapsulation of polymeric material filled with solid or liquid drug or with suspension of drug in fluid; heterogeneous dispersion of drug particles in a solid biodegradable or non biodegradable matrix; laminate of agent and polymeric material made by coating a film of biodegradable or non biodegradable material with solid drug and then forming the film into a sealed sandwich; a heterogeneous dispersion or solution of drug in a water swellable hydrogel matrix which controls drug release by slow surface to center swelling of the matrix by water; liquid-to-liquid encapsulation of drug in a viscous solution of polymer which controls drug release by slow diffusion through dilution of the media; pumps that either mechanically or chemically provide drug ;drug coated micropellets which have an apparent density lower than that of gastric juice; drug containing bioadhesive polymer that adheres to the mucin coating of the GI tract and which is retained on the surface epithelium to extend GI transit of the drug; chemical bonding of drug

to polymer backbone by amide or ester linkages which control drug release by hydrolysis and the formation of macromolecular structures of the drug via ionic or covalent linkages which control drug release by hydrolysis, thermodynamic dissociation or microbial degradation and formation of macromolecular structures of the drug via ionic or covalent linkages, which controls drug release by hydrolysis, thermodynamic dissociation, or microbial degradation.

The principles underlying drug release from the various fabrications are diffusion controlled release (Flynn, 1974), dissolution controlled release (Carstensen, 1977), diffusion and dissolution controlled release (Javaid *et* al., 1971; Kallstrand and Ekman, 1979), ion-exchange controlled release (Raghunathan *et al*., 1981), pH independent formulations (Sanchez-Lafuente, 2002), osmotically controlled release (Theeuwes, 1984) and altered density formulations (Sheth and Tossounian, 1984).

Regardless of the mechanism of sustained release the majority of oral sustained release formulations rely on polymers, used as coating or matrix systems from which drug release is controlled. There is currently growing popularity of hydrophilic matrix systems for controlled release. Matrix systems are easy to formulate, by direct compression, dry granulation and wet granulation tabletting; are easy to produce with existing, conventional equipment and processing methods as tablets or capsules. Compared to other controlled release drug forms hydrophilic matrix systems are simpler and more economical to manufacture.

Voltarol Retard tablets consist of diclofenac sodium embedded within a simple wax matrix and film coated, giving a slow-release formulation. The main objective of this study was the formulation of film-coated SR diclofenac sodium tablets 100 mg using a mixture of HPMC and NaCMC as the hydrogel matrix control agents, with diclofenac sodium release profiles similar to that of Voltarol Retard tablets 100 mg.

MATERIALS AND METHODS

Materials

Diclofenac sodium (Secifarma, Italy), HPMC E15 (Colorcon, US), NaCMC (BDH Chemicals, UK), Aerosil 200 (Degussa, France), magnesium stearate (BDH Chemicals, UK), stearic acid, ethylcellulose, diethylphthalate, titanium dioxide, red iron oxide, methanol and dichloromethane (BDH Chemicals, UK) were used as received from their manufacturers.

The composition of the diclofenac sodium hydrogel tablets prepared in this study was as follows:

Table 1: Compositions of the tablets

BATCH	DF1	DF2	DF3	DF4
Diclofenac sodium	100 mg	100 mg	100 mg	100 mg
HPMC DOW E15	250	150	225	140
NaCMC	25	16	22.5	14
Aerosil 200	3.5	2.5	3.5	2.5
Magnesium stearate	1.75	1.5	1.75	1.25
Stearic acid	0	0	1.75	1.25
Target tablet weight	380.25	270	270	259
Average weight of tablets	368	270	347	250
Weight uniformity	3.5%	3%	-	-
Hardness, KP	6-10	8-9	5-8	5-6
Comments	Slight sticking tendency	Slight sticking tendency	Sticking persists with addition	Sticking persists with addition

			of stearic acid	of stearic acid.

Compression of tablet cores

A batch size of 2 kg tablets was prepared for each tablet formulation. In preparing the tablets, the ingredients were first screened through a 500 µm 30 mesh BS screen before weighing. Then, all the weighed quantity of diclofenac sodium, HPMC, Na CMC, half the amount of Aerosil 200 and two- thirds the amount of magnesium stearate were blended and compressed into slugs. The resulting compacts were passed through a comminuting mill fitted with 1.5 mm screen. The resulting mass was blended with the remaining half of Aerosil 200 and third portion of magnesium stearate and screened through a 30 mesh screen before compression into tablets using a Manesty F3 tabletting machine (Manesty Machines, Manchester, UK) fitted with 11 mm normal concave tooling to a target tablet weight of 414 mg.

Film coating of tablet cores

The tablets were film-coated in a laboratory scale Manesty Accelacota (Manesty Machines, UK). The composition of the coating mixture used was as follows:

Ethyl cellulose 10 cp	10 g
HPMC 5 cp	10 g
HPMC 15 cp	40 g
Diethyl phthalate	10 g
Titanium dioxide E171	10 g
Red iron oxide E172	0.7 g
Methanol	0.8 L
Dichloromethane	1.2 L

A 5 L volume of the mixture was prepared for the coating process.

In the film coating experiments the following process parameters were used:

Inlet and bed temperature:
60^oC

Relative humidity:	60% RH
Atomization air pressure:	300 kPa
Liquid spray rate:	2.8 rpm
Drying time:	15-30 min

The tablets were preheated for 5 min until the drum temp was 40oc, and the rotating speed of the drum adjusted to 3 rpm for the preheating and post-drying steps. After being sprayed, the tablets were dried for 6 min at 40 ^oC in the drum coater. The tablet cores were coated to a final weight of about 435 mg. Thereafter, the film coated tabs were kept at a controlled RT (25^oC and 60% RH) for at least 24 h before analysis. The thickness of the coating (35-40 um) was estimated from the increase in the tablet height (n=10) which was measured with a digital micrometer (Sony Micrometer, Sony Magnescale Inc, Tokyo, Japan).

Dissolution studies on tablets

Diclofenac sodium release rates from the dosage forms were monitored over a 12-h period using an automated Philips PU8620 Tablet Dissolution System (Philips Instruments, UK). A 1000 ml volume of 0.05 M phosphate buffer maintained at 37^0C was used as the dissolution medium. The spindle of the dissolution apparatus was fixed to rotate at 60 r.p.m. and the tablets were prevented from floating by the aid of a stainless steel helical spring.

Analysis for the drug content of samples of the dissolution medium was performed on-line in a UV/VIS spectrophotometer coupled to the dissolution tester. The absorbance of diclofenac sodium was measured at

308 nm with a. Percent drug released was plotted as cumulative percent drug dissolved against time and each datum point represents the average of 4 tablets.

RESULTS AND DISCUSSION

Geigy's Voltarol Retard 100 mg tablets, is a drug with a master file record and other SR formulations are compared to it. Therefore, the dissolution profiles of hydrogel tablets containing HPMC and NaCMC formulated in the study were compared with those of Voltarol retard 100mg tablets.

The releases of diclofenac sodium from formulations prepared in the study are presented in Figs 1-4. In Fig 1, all the formulations exhibited SR profiles with the Voltarol tablets exhibiting more diclofenac sodium release than the hydrogel tablets. The profiles of the hydrogel tablets suggest that two rates of drug release are operational, the first from 0 – 9 h, and a second rate after 9 h of dissolution testing. In Fig 2, all the formulations show SR release of diclofenac sodium with release from Geigy's Voltarol tablets again greater than that from the hydrogel tablets. In Fig 3, drug release from the hydrogel tablets was greater compared to release from the Voltarol tablets. In Fig 4 all the tablet formulations exhibited SR. The main difference in the hydrogel formulations was the ratio of HPMC to NaCMC used. On the basis of the dissolution profiles obtained with the hydrogel tablets, it is reasonable to suggest that the hydrophilic polymers can be used in appropriate combinations to formulate SR tablets containing diclofenac sodium.

Since the primary aim of this study was a feasibility of using the HPMC and NaCMC mixture available to us in the formulation of SR tablets, it was necessary to suggest the main mechanism of drug release from the formulations. In this system, a solid drug was dispersed in hydrophilic matrix. The rate of drug release was dependent on the rate of drug diffusion but not on the rate of solid dissolution. Higuchi (10) has described the appropriate equation describing drug release from this type of system as $Q = [De/T (2A - e C_s) C_s t]^{1/2}$ where Q= wt in grams of drug released per unit surface area; D = diffusion coefficient of drug in the release medium; e = porosity of the matrix; T = tortuosity of the matrix; C_s = solubility of the drug in the release medium; and A = concentration of drug in the tablet expressed as g/ml.

For purposes of data treatment the Higuchi equation reduces to $Q = k t^{1/2}$ and a plot of amount of drug released from the matrix versus the square root of time should be linear if drug release from the matrix is diffusion controlled. Drug release from all the formulations investigated in this study assumed similar shape and pattern and a typical plot of diclofenac sodium release from the matrix in phosphate buffer is shown in Fig. 5. The plot is linear and suggests that in the hydrogel tablets prepared and evaluated, diffusion control is the predominant mechanism of drug release. Detailed investigation of other mechanisms of diclofenac release as well as the optimization of the formulations and pilot scale up of the lead formulation is in progress.

CONCLUSION

It is possible to use HPMC and NaCMC in the formulation of

sustained release diclofenac sodium tablets with dissolution profiles similar to that of Voltarol Retard tablets. However, Voltarol Retard tablets consist of diclofenac sodium embedded within a simple wax matrix and film coated, giving a slow-release formulation while the hydrophilic matrix agents HPMC and NaCMC used in the study may be responsible

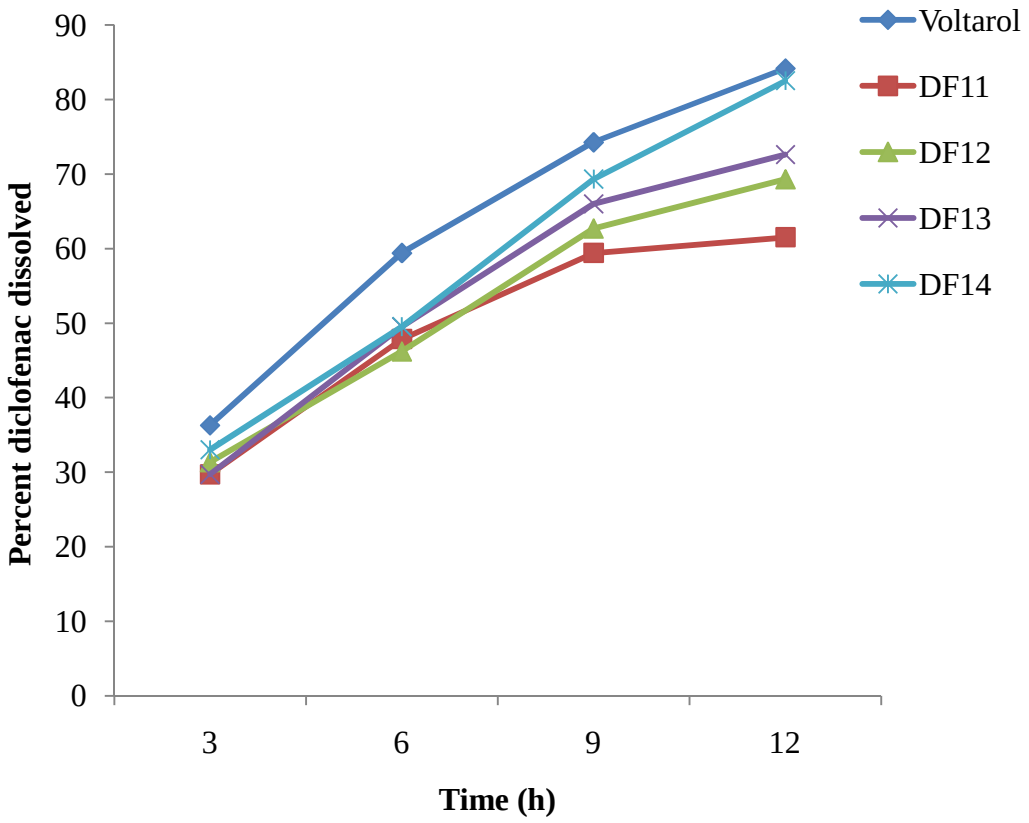

Fig. 1: Dissolution profiles of SR diclofenac sodium hydrogel tablets 100 mg in 0.05 M phosphate buffer (pH 7.5) using USP dissolution apparatus paddle mathod at 60 r.p.m.

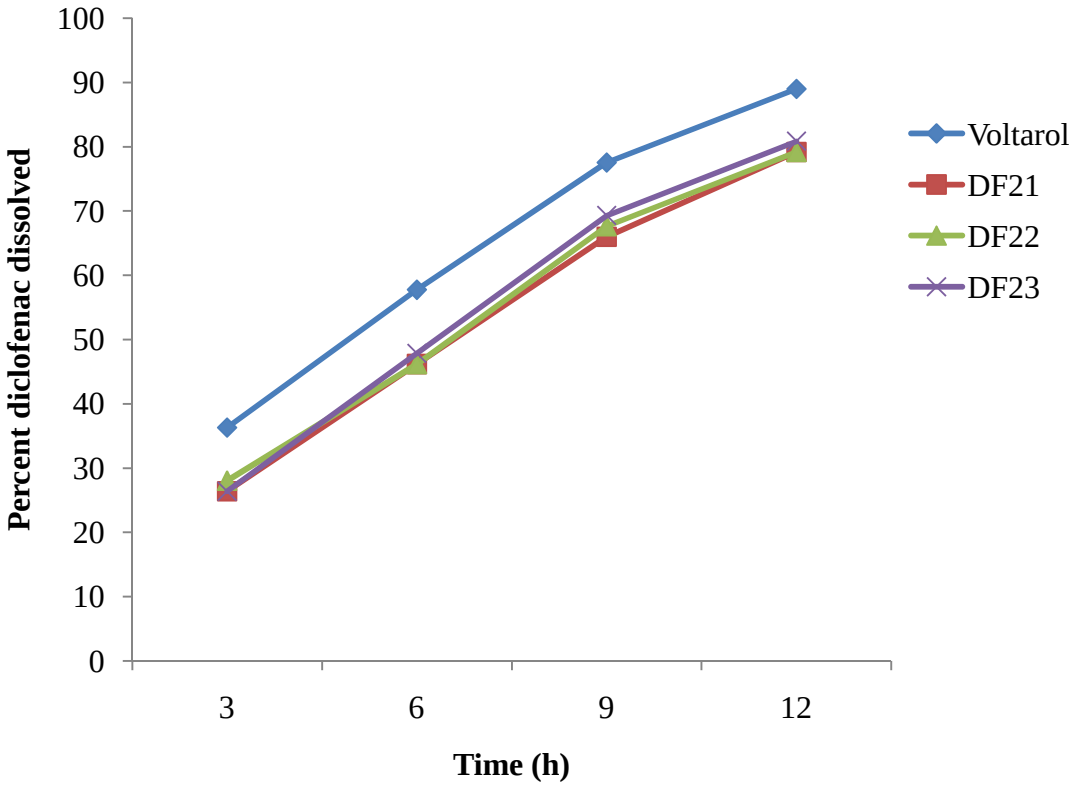

Fig. 2: Dissolution profiles of SR diclofenac sodium hydrogel tablets 100 mg in 0.05 M phosphate buffer (pH 7.5) using USP dissolution apparatus paddle method and 60 r.p.m.

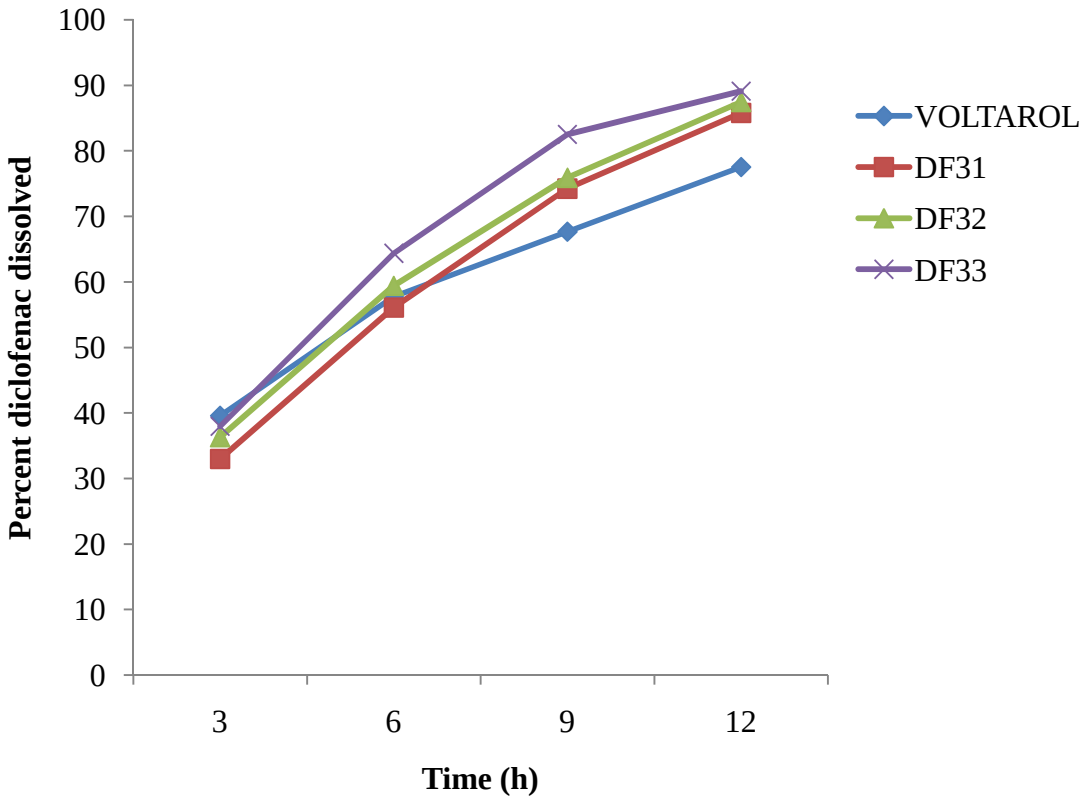

Fig. 3: Dissolution profiles of SR diclofenac sodium hydrogel tablets 100 mg in 0.05 M phosphate buffer (pH 7.5) using USP dissolution apparatus paddle method and 60 r.p.m.

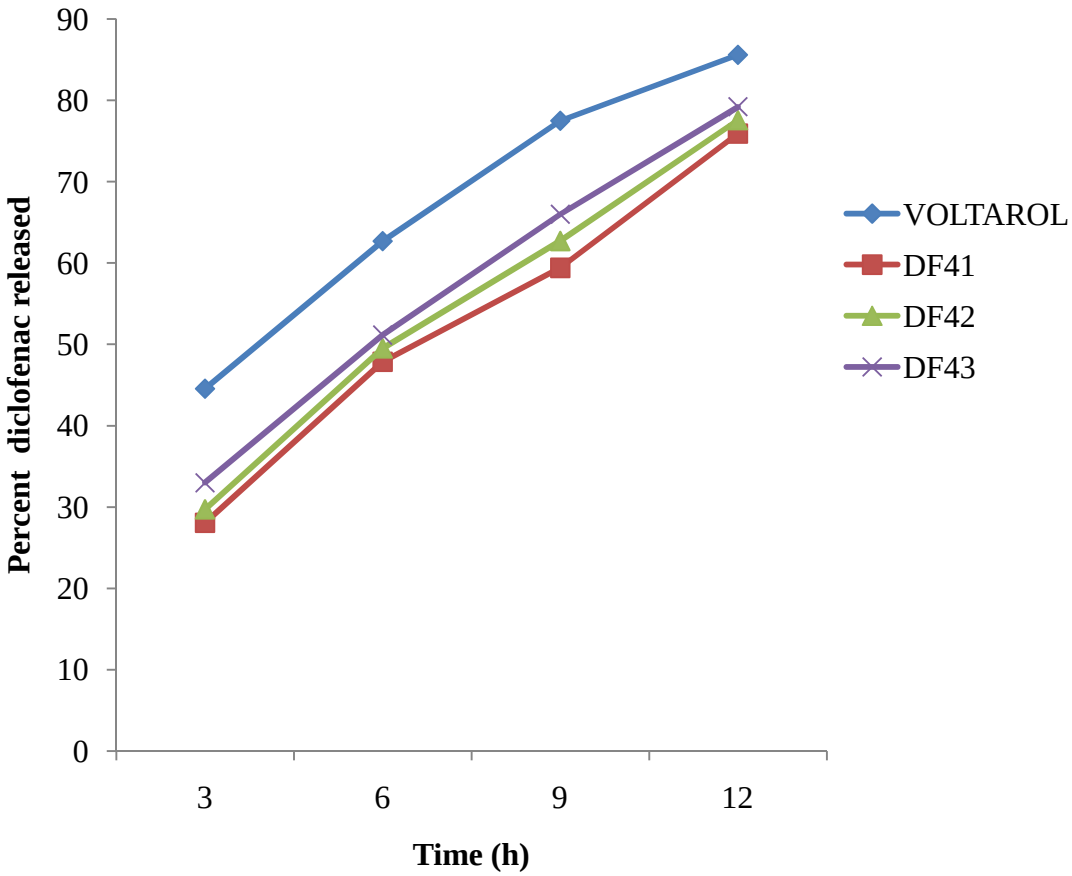

Fig. 4: Dissolution profiles of diclofenac sodium SR hydrogel tablets 100 mg in 0.05 M phosphate buffer (pH 7.5) using USP dissolution apparatus paddle method and 60 r.p.m.

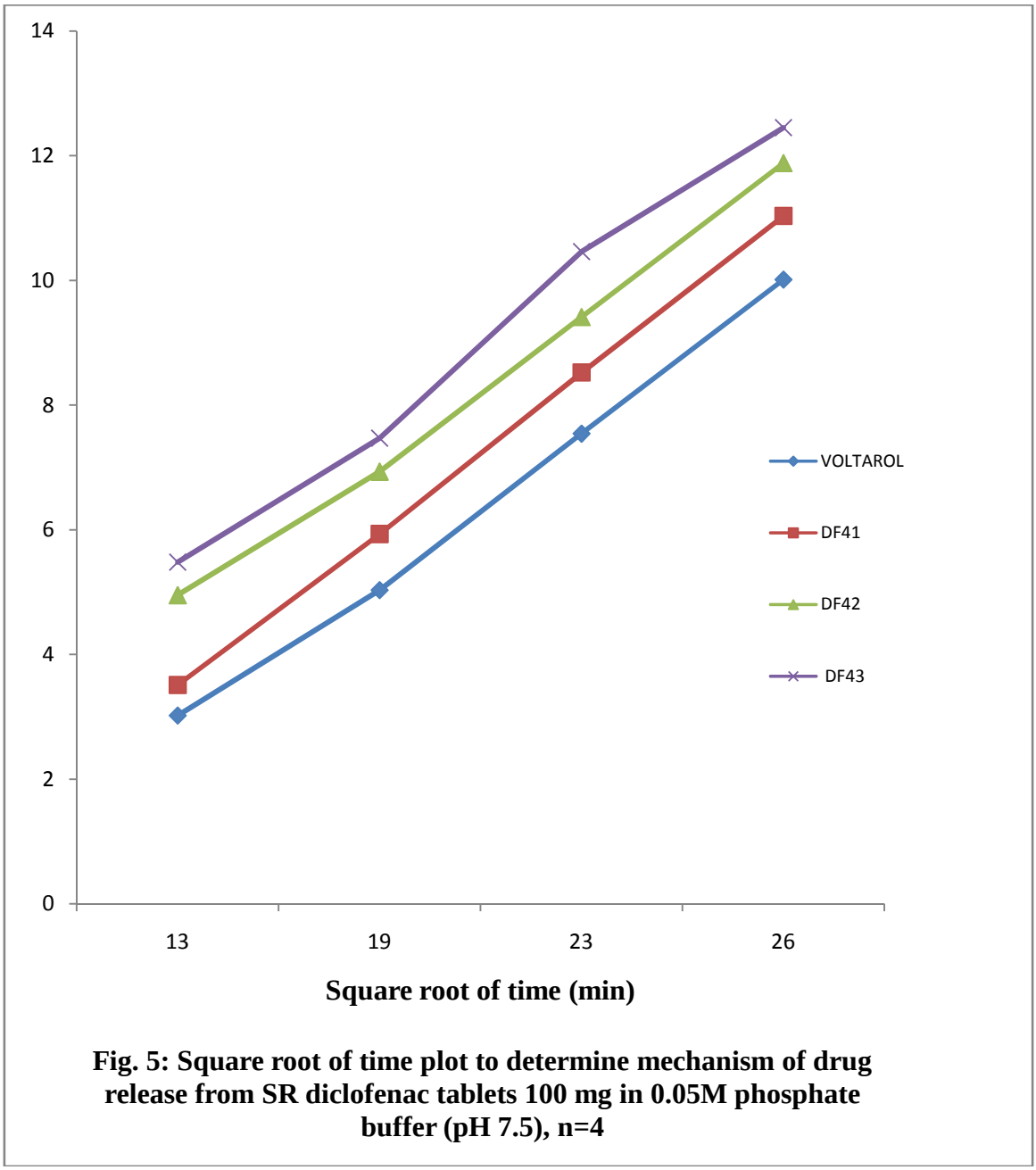

Fig. 5: Square root of time plot to determine mechanism of drug release from SR diclofenac tablets 100 mg in 0.05M phosphate buffer (pH 7.5), n=4

for the differences observed. The shape of dissolution profiles obtained with the hydrogel tablet formulations was similar to that of Voltarol tablets up to 9 hours of dissolution testing, thereafter; it is obvious that different mechanisms of drug release became operational in the hydrogel tablets.

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