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Research Article

A COMPARATIVE STUDY OF EFFECT OF HYDROPHILIC POLYMERS ON DISSOLUTION RATE OF ACECLOFENAC

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ABSTRACT

Biopharmaceutics Classification System (BCS) takes into account solubility and intestinal permeability. The BCS has proven to be a very helpful and widely accepted starting point for pharmacological product development and regulation in the pharmaceutical industry. Aceclofenac is a nonsteroidal anti-inflammatory medication (NSAID) that is used to treat inflammation. Osteoarthritis, rheumatoid arthritis, dysmenorrhoea, acute lumbago, musculoskeletal trauma, and gonalgia are among the conditions for which it is commonly recommended. To manufacture prolonged release matrix tablets, hydrophilic polymers are often employed. The persistent action of these polymers was demonstrated by the formation of a thick gel layer around the matrix. This gel layer is critical in regulating the medication's release in the tablet's body. The purpose of this research is to formulate, optimise, and evaluate the effect of various hydrophilic polymers such as hydroxypropyl methyl cellulose (HPMC), hydroxyethyl cellulose (HEC), polyvinyl pyrrolidone (PVP) of various viscosities such as PVP K25, PVP K30, PVP K90, and polyethylene glycol (PEG-4000) on the dissolution rate of aceclofenac in various ratios of 1:4, 1:8 and 1:12. To manufacture prolonged release matrix tablets, hydrophilic polymers are often employed. The persistent action of these polymers was demonstrated by the formation of a thick gel layer around the matrix. This gel layer is critical in regulating the medication's release in the tablet's body.

Keywords: Aceclofenac, Tablets, Hydrophilic polymers, Dissolution.

1. INTRODUCTION

About 40% of newly discovered chemical entities are lipophilic, and due to their poor aqueous solubility, they never make it to market. The increase of oral bio-availability of weakly water-soluble medicines is one of the most difficult elements of medication development. In drug research, product development, and drug product regulatory sciences, the Biopharmaceutics Classification System (BCS) has proven to be quite useful. The classification scheme takes into account the two most important characteristics that influence oral drug absorption: solubility and intestinal permeability, and it has proven to be a very helpful and widely accepted starting point for pharmacological product development and regulation [1, 2].

Aceclofenac is an NSAID with a multifactor mode of action. The primary mechanism of action is to suppress prostaglandin production (PG) ACE prevents the production of inflammatory cytokines, interleukins, and tumour necrosis factors. Aceclofenac has a low water solubility (0.058g/ml), which makes it difficult to dissolve and absorb. The biopharmaceutical classify-cation system (BSC) divides all treatment candidates into four classifications based on their solubility and permeability. Aceclofenac is a BSC class II chemical, and its oral bioavailability is determined by the rate at which it dissolves in the gastrointestinal system. As a result, enhancing the bioavailability and therapeutic efficacy of aceclofenac requires better dissolving [3, 4].

Size reduction, surfactant use, pH adjustment, complexation, prodrug, nanomization, liposome manu-facturing, and solid dispersion development are all commonly used methods for increasing the solubility and bioavailability of poorly water-soluble drugs [5-7].

Angle of repose, bulk density, tapped density, compressibility index, and Hausner's ratio on granules formed by a physical mixing procedure as part of the preformulation process were investigated [8]. The hardness, friability, disintegration time, wetting time, water absorption ratio, medication content, and cumulative percentage release of the tablets were all assessed. According to the findings, tablets containing the polymer HPMC K25, PEG4000, PVP K25, PVP K30 and PVP K90 had an outstanding dissolving profile [9]. The drug concentration of all formulations was within permissible ranges, according to the Indian Pharmacopoeia of 2007. This research helped researchers better understand the impact of hydrophilic polymers on the dissolving profile of a water-insoluble medicine (BCS class II drugs). Drugs that are poorly water soluble are classified as BCS classes II and IV [10, 11]. For lipophilic medicines, dissolution is the rate limiting stage in the absorption process via the oral route. The influence of several hydrophilic polymers on the dissolution profile of Aceclofenac was investigated.

2. MATERIAL AND METHOD

2.1. Material

Aceclofenac was obtained as a kind gift sample from Necro Pharmaceuticals Pvt. Ltd., Mumbai. Hydroxy-propyl Methylcellulose K25 (Colorcon Asia Pvt. Ltd., Singapore), Polyvinyl Pyrrolidone K25, K30, K90, and microcrystalline cellulose, Avicel pH102 (FMC bio-polymer, U.S.A.), PEG 4000 (BASF Corporation, USA) were procured from Vineet Pharma. Pvt. Ltd., Indore. All the other ingredients used in formulation including D-mannitol, Sodium Saccharine, Magnesium stearate and Talc were of laboratory grade.

2.2. Method

A weighed amount of material was kneaded to a paste consistency in a mortar moistened with water. Following that, a weighed amount of drug was gently milled for 30 minutes. A sufficient amount of water was added during this operation to maintain the desired consistency. Finally, after passing through a 60-mesh size screen, the resulting paste was dried in a water bath at 40°C until the water was fully removed and kept in desiccators over fused calcium chloride. The kneading procedure was used to create formulations, as shown in table 1.

2.3. Determination of maximum wavelength absorption

A UV-Vis spectrophotometer was used to measure the samples at 277 nm after they were filtered (UV-1700, Shimadzu, Japan). We utilised a standard curve made with pure active medication to determine the concentration of the sample [12].

Table 1: Composition of aceclofenac tablets using various hydrophilic polymers

Ingredient (mg)	Batch									
	A0	AH1	AH2	AH3	AE1	AE2	AE3	AV1	AV2	AV3
Aceclofenac	100	100	100	100	100	100	100	100	100	100
HPMC K25	--	4	8	12	--	--	--	--	--	--
PEG 4000	--	--	--	--	4	8	12	--	--	--
PVP K25/K30/K90	--	--	--	--	--	--	--	4	8	12
MCC	50	50	50	50	50	50	50	50	50	50
Mannitol	34	22	18	14	22	18	14	22	18	14
Na. Saccharine	10	10	10	10	10	10	10	10	10	10
Talc	4	4	4	4	4	4	4	4	4	4
Mag. Stearate	2	2	2	2	2	2	2	2	2	2
Total Weight (mg)	200	200	200	200	200	200	200	200	200	200

A0- Formulation without any hydrophilic polymer, AH- Formulation containing HPMC K25, AE- Formulation containing PEG4000, AV- Formulation containing PVP K25/K30 or K90.

2.4. Drug-Excipient Compatibility Study

Compatibility studies were conducted by generating compatibility blends with varying excipient-to-drug ratios based on a tentative average weight to analyse and anticipate physicochemical interactions between drug material and excipients. These combinations were stored at 40°C for a month with 75% as a relative humidity [13]. The drug-to-excipient ratio is typically between 1:4, 1:8 and 1:12. To see if any physical properties had altered, the samples were compared to a

control sample held at 40°C for 7, 14, and 30 days [14]. FTIR spectrometry, which measures chemical compatibility, is the most powerful method for locating medication functional groups. In this study, the potassium bromide disc (pellet) method was applied.

2.5. Dissolution study

The USP dissolution test apparatus-II was used to study the dissolution of aceclofenac from various tablet processes in 900 mL of water at 37.5°C with a paddle stirrer at 100 rpm for 60 minutes. 5 ml of the sample was extracted and replaced with fresh 5 ml dissolving fluid at predefined time intervals using a syringe fitted with a prefilter. By measuring the absorbance at 277 nm, these samples were evaluated for the presence of aceclofenac [15].

2.6. Characterization of powder blends of active pharmaceutical ingredient and excipients

Angle of repose, bulk density, tapped density, compressibility index, and Hausner's ratio were all measured for the powder blend [8].

2.6.1. Angle of repose

The funnel method was used to determine the angle of repose of API powder. The maximum angle that can be reached between the surface of a pile of powder and the horizontal plane is called the angle of repose. The powder combination was weighed and placed into the funnel with precision. The height of the funnel has been reduced to 2.5 cm above ground level. Allow for free flow of the powder mixture through the funnel and onto the surface. The diameter of the powder cone is measured three times to provide an average value.

The equation is used to calculate the angle of repose:

Angle of Repose (θ) = $\tan^{-1}[h/r]$

Where, h = height of pile, r = radius of the base of the pile, θ = angle of repose.

2.6.2. Bulk density determination

The mass to volume ratio of an untapped powder sample determines a substance's bulk density (including inter particulate void volume). The powder (W) was weighed and placed in a graduated measuring cylinder to calculate the volume (V0). The formula used to compute bulk density is given below:

Bulk density (BD) = $[W/V_0]$

Where, W=Weight of powder, V_O=Volume of powder.

2.6.3. Tapped density determination

The tapped density is obtained by mechanically tapping a graduated cylinder containing the sample until only a minor volume change is seen. The powder sample weighing 25 gm was screened using sieve No.18, and the weight of the sample was placed in a 100 mL graduated cylinder. A tapped density tester was used to mechanically tap the cylinder 500 times at a nominal rate, and the tapped volume Vo was recorded. When the difference between two tapping volumes is less than 2%, Vf is tapped volume. The blend volume was used to compute the tapped density, Hausner's ratio, and Carr's Index. The unit of bulk density and tapped density is g/ml.

The formula used to calculate tapped density is given below:

Tapped Density (TD) = $[W/V_f]$

Where, W = Weight of powder, Vf = Volume of powder.

2.6.4. Carr's index

Carr's index is described by the term compressibility. It's a metric for how compressible a powder is. It is linked to relative flow rate, cohesion, and particle size in an indirect way.

The formula for calculating Carr's index was:

Carr's Index (%) = {(Tapped Density-Bulk Density)/ Tapped Density}x 100

2.6.5. Hausner's ratio

Hausner's ratio, which indicates the flow properties of the powder, is calculated using the ratio of tapped density to bulk density.

Hausner's Ratio = Tapped Density/Bulk Density

2.7. Evaluation of Prepared Tablets [16]

2.7.1. Thickness

With a Vernier calliper (Mitutoyo 500-196-30-Advanced), the thicknesses of the tablets were measured, and average values were calculated using 20 tablets from each batch.

2.7.2. Uniformity of weight

Each tablet in a batch should be of the same weight, and weight deviations should be within the pharmacopeia's allowed acceptable range. A Mettler Toledo AB analytical balance, model AB104-S, was used to determine weight uniformity. The weight variation was determined using a sample of ten tablets.

2.7.3. Hardness

The tablet's hardness reflects its durability. A hardness tester (Erweka, TBH 425) was used to determine the hardness of 10 tablets from each batch.

2.7.4. Friability

Using the friability test instrument, the friability of 10 tablets for each formulation was determined (Electrolab, EF-2W).

2.7.5. In vitro dissolution test

Dissolution tests on the manufactured tablets were carried out using the Electro lab apparatus II. At 37 ± 0.5°C and 100 rpm, dissolution was carried out in 900 mL of pH 6.8 phosphate buffer. An autosampler (UV spectrophotometer Shimadzu, UV1900i) linked to the dissolution apparatus was set to extract and replenish 5 ml of the dissolution media at 0, 2,4,6,8,10,12,15 and 18 hours and drug release was measured at 277 nm.

3. RESULTS AND DISCUSSION

3.1. Evaluation of granules

In the granules of all formulations, angle of repose, bulk density, tapped density, compressibility index, and Hausner's ratio were all measured. Table 2 summarises the evaluation parameters. The granules are free-flowing, according to all of these studies.

3.2. Evaluation of tablets

The tablets' average weight was found to be between 197.1±1.08 to 202.3±1.42 mg. Thickness ranges from 3.12±0.28 to 4.14±0.46 mm, hardness ranges from 4.632±0.10 to 5.653±0.57 kPa, and friability ranges from 0.38 to 0.82 percent. Table 3 summarises all of these variables.

Table 2: Evaluation of pre-compression parameters for granules

Parameter	Drug: HPMC			Drug: PEG 4000			Drug: PVP K25			Drug: PVP K30			Drug: PVP K90		
	1:4	1:8	1:12	1:4	1:8	1:12	1:4	1:8	1:12	1:4	1:8	1:12	1:4	1:8	1:12
Angle of repose (θ) degrees	35.72	36.42	38.14	33.13	34.32	32.11	28.61	37.31	29.15	35.53	38.65	31.84	32.31	36.27	27.19
Bulk density (gm/ml)	0.28	0.34	0.31	0.35	0.29	0.29	0.31	0.33	0.37	0.31	0.29	0.33	0.32	0.36	0.33
Tapped density (gm/ml)	0.34	0.37	0.36	0.47	0.41	0.42	0.43	0.44	0.49	0.43	0.36	0.43	0.46	0.42	0.44
% Compressibility index	16.49	7.2	14.48	24.98	28.58	30.77	27.25	23.12	24.99	28.57	20.01	18.02	30.39	14.13	24.90
Hausner's ratio	1.19	1.07	1.17	1.33	1,40	1.44	1.3	1.32	1.13	1.4	1.2	1.3	1.4	1.16	1.33

Table 3: Evaluation of tablets

Parameter	Drug: HPMC			Drug: PEG 4000			Drug: PVP K25			Drug: PVP K30			Drug: PVP K90		
	1:4	1:8	1:12	1:4	1:8	1:12	1:4	1:8	1:12	1:4	1:8	1:12	1:4	1:8	1:12
Thickness (mm) n=10	3.14 ±0.09	3.93 ±0.17	4.14 ±0.46	3.32 ±0.13	3.12 ±0.28	3.83 ±0.36	3.55 ±1.10	3.25 ±0.25	3.70 ±0.82	3.54 ±0.62	3.13 ±0.83	3.74 ±0.90	3.64 ±0.14	3.93 ±0.12	4.14 ±0.36
Average Wt. (mg) n=10	201.9 ±1.35	200.3 ±0.47	199.8 ±2.15	200.4 ±2.35	198.4 ±1.42	202.1 ±1.03	202.3 ±1.42	201.4 ±0.67	198.2 ±1.15	197.1 ±1.08	201.1 ±0.95	199.4 ±1.75	202.1 ±1.35	200.1 ±0.47	198.1 ±2.15
Hardness (kPa) n=10	5.172 ±0.20	5.616 ±0.47	5.157 ±0.15	4.632 ±0.10	4.831 ±0.42	5.053 ±0.15	4.672 ±0.17	4.810 ±0.47	5.051 ±0.24	5.072 ±0.79	5.213 ±0.27	5.153 ±0.96	5.272 ±0.21	5.412 ±0.27	5.653 ±0.57
Friability (%)	0.62	0.57	0.38	0.53	0.82	0.58	0.72	0.57	0.82	0.72	0.63	0.81	0.72	0.64	0.48

The thickness of all formulations was uniform, the tablet hardness was acceptable, and the percentage friability for all formulations was less than 1%, showing that friability was within acceptable limits. Good and homogenous drug content (>95%) was reported within batches of various tablet formulations.

3.3. Dissolution of Formulations

All the formulations were tested in vitro using pH 6.8 phosphate buffer solution for dissolution study for 18 hours. The dissolution of tablets using various polymers like HPMC, PEG4000, PVP K25, PVP K30 and PVP K90 is given in figure 1. The samples were analyzed using an autosampler (UV spectrophotometer Shimadzu, UV1900i) linked to the dissolution apparatus.

Water solubility is a problem for many medications created in recent years. Improving the dissolving rate of weakly water-soluble medicines is a good way to improve their gastrointestinal absorption after oral administration. In this study, a ground mixture of Aceclofenac, a poorly water-soluble drug, and hydrophilic polymers such as HPMC, PEG-4000, PVP

K25, PVP K30, and PVP K90 was prepared, and the effect on dissolution behaviour of Aceclofenac was evaluated to provide information to aid in the development of novel oral formulations.

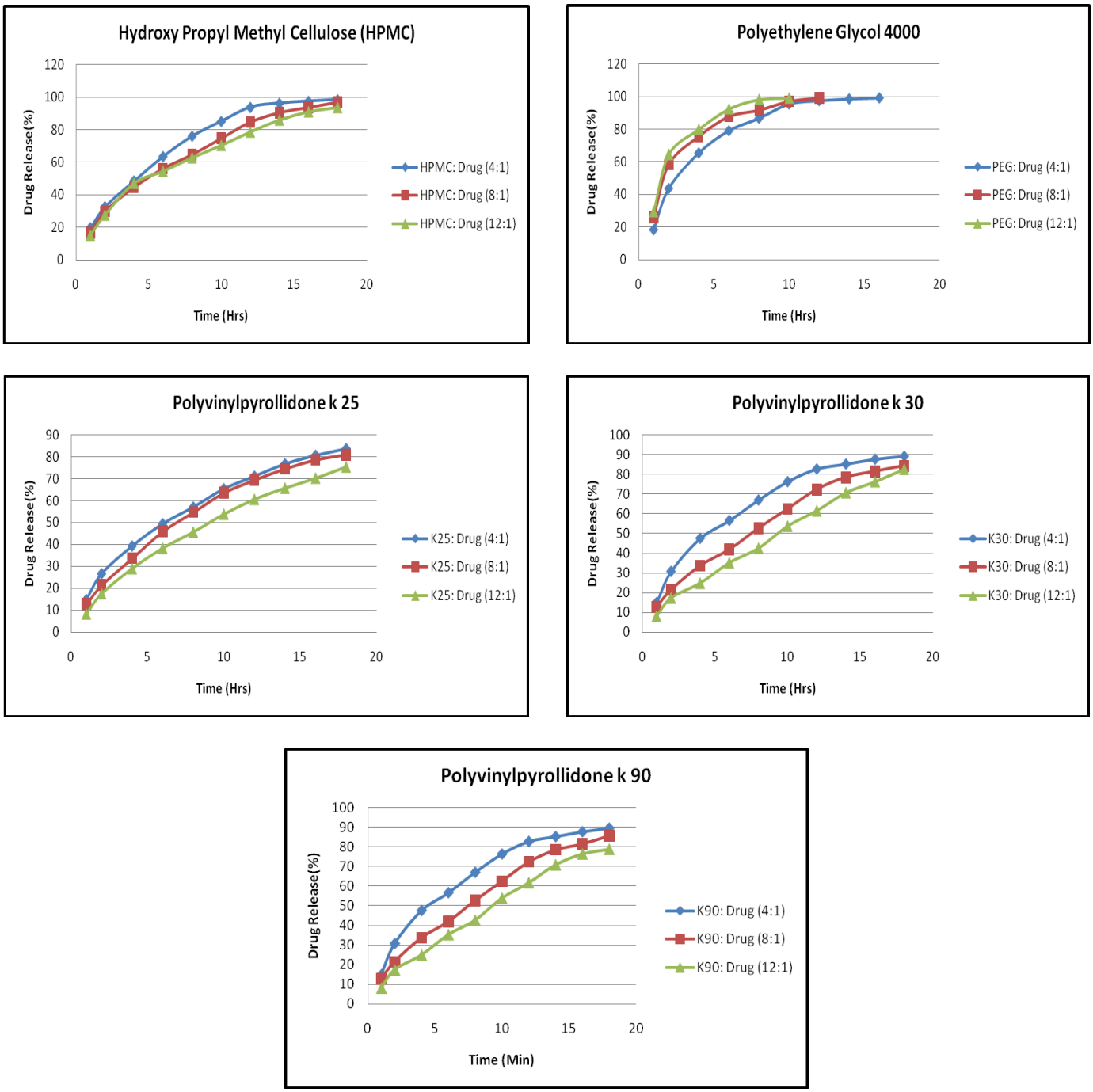

Fig. 1: Dissolution profile of Aceclofenac using various hydrophilic polymers

In the present work the preformulation study of physical mixture with the hydrophilic polymers and drug at the different rations (1:4, 1:8, 1:12) exhibits some evaluation regarding the flowability, bulk density and tapped density of the powder mixture. The Carr's index, Hausner's ration and Angle of repose results evaluated for the flowability study. The flowability decreases in the sequence of PEG 4000>HPMC>PVP K25>PVP K30>PVP K90.

The hydrophilic polymers having the property of the drug release in the sustained manner with the different mechanism like HPMC shows the gel formation, PVP

shows the viscosity improvement etc. In the present study the sustainability order was found to be PVP K90>PVP K30>HPMC> PVP K25>PEG 4000.

The *in vitro* dissolution performance of Aceclofenac in phosphate buffer at pH 6.8 was studied. In the case of PVP K30 and PVP K90, the dissolution rate and saturation solubility of Aceclofenac increased with the concentration of the polymers. Also, in the formulation including the PEG 4000 and PVP K25 were less concentration dependent and HPMC was found to be concentration independent.

The hydrophilic polymers PVP K30 and PVP K90 are showing the increasing sustainability as compare to the HPMC and PEG 4000. The cumulative drug release in the order of PEG 4000>PVP K25>HPMC>PVP K30>PVP K90.

4. CONCLUSIONS

In the present study we have analyzed the effect of different hydrophilic polymers (one of the methods of improving the dissolution of the poorly water-soluble drugs) effect on the dissolution profile of the Aceclofenac, BCS class II drug. In the present study the flowability of the physical mixture (Drug: Polymers) was found to be in the order:

PEG 4000>HPMC>PVP K25>PVP K30>PVP K90.

The sustainability order is:

PVP K90>PVP K30>HPMC> PVP K25>PEG 4000.

The cumulative drug release in the order of:

PEG 4000>PVP K25>HPMC>PVP K30>PVP K90.

These results concluded that the different kinds of hydrophilic polymers are having the different properties and possess innovative mechanism of action for the drug dissolution. In the study it was found that polymers like PVP K30 and PVP K90 are showing concentration dependency which is beneficial in the determination of concentration of polymers in the formulation as per the requirement (like in sustained release and extended-release formulation). Similarly other polymers like PEG 4000 and PVP K25 are showing somewhat concentration independency and which is also having the highest drug release rate in the formulation which is having beneficial use in the tablet formulation.

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Conflicts of interest

There are no conflicts of interest.

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