

Original Article

## INFLUENCE OF DRUG SOLUBILITY AND POLYMERS SUPPLY SOURCE ON THE PHYSICAL PERFORMANCE OF MATRIX TABLETS

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### ABSTRACT

**Objective:** The aim of this study is to explore the possible effects of drug solubility and commercial supply sources of HPMC and PVP on physical properties of matrix tablets.

**Methods:** Two different supply sources (A and B) for Hydroxy Propyl Methyl Cellulose (HPMC) as matrix forming polymer and Polyvinyl Pyrrolidone (PVP) as matrix supportive polymer were used with either Chlorpheniramine maleate (CPM), as a water soluble drug or Atenolol (ATN), as a water insoluble drug, to produce a series of matrix formulations using direct compression according to a 2<sup>3</sup> full factorial design. Matrices were then qualified for friability, hardness, and drug release attributes.

**Results:** Matrix hardness and friability properties demonstrated to be influenced by PVP supply source as an individual factor alone or in combination with drug solubility factor, moreover, both properties were found to be less affected by drug solubility and HPMC supply source, as individual factors. Compared to other factors, drug solubility was found to have a substantial influence on drug dissolution efficiency (DE) and diffusion exponent of the drug release (n) of different matrices.

**Conclusion:** Variation in commercial PVP supply source and drug solubility could possibly result in matrices with different physical performance.

**Keywords:** Drug solubility, HPMC supply source, PVP supply source, Matrix hardness, Matrix friability, Matrix release.

### INTRODUCTION

Polymers are substances or materials that have a high molecular weight and consisting of repeated units named as monomers. Pharmaceutical applications of polymers are numerous and cover a wide range of utility [1,2]. This might be attributed to their biodegradability, pharmacological inertness, compatibility and low cost. The wide range of physicochemical properties offered by these materials may be utilized to improve both the clinical and non clinical (e. g., manufacturing, stability) properties of dosage forms.

Polymers can be categorized into two classes, water soluble (hydrophilic) and water insoluble (hydrophobic) polymers. Hydroxypropyl methyl cellulose (hypromellose, HPMC) is a hydrophilic polymer available in several grades that vary in viscosity and extent of substitution. It is widely used in oral, ophthalmic and topical pharmaceutical formulations [3].

Polyvinylpyrrolidone (PVP) is a hydrophilic polymer available in several grades. In addition to utilization of PVP in tablets production, it is used as a suspending, stabilizing, or viscosity increasing agent in a number of topical and oral suspensions and solutions.

Incorporation of a drug in a polymeric matrix is one of the methods to develop controlled release dosage forms. The widespread application of the matrix as a dosage form for non conventional drug delivery is attributed to simplicity, versatility and reproducibility of its fabrication method.

Numerous researches dealing with the pharmaceutical application of HPMC in matrices for sustained release drug delivery have been reported [4-6] and addition of PVP-K30 in HPMC-based matrix is believed to support the matrix for constant drug release through enhancing swelling-erosion balance of the matrix [7].

Many factors have been reported to affect the performance and drug release of matrix tablets [8,9]. However, the individual or mutual influences of drug solubility and the commercial supply source of polymers on matrix performance have received less attention among formulation scientists.

The objective of this study is to explore the possible effects of drug solubility and supply source of included polymers (HPMC K4M and PVP K-30) on the characteristics of matrix tablets using Atenolol and Chlorpheniramine maleate as sparingly and free water soluble model drugs, respectively.

### MATERIALS AND METHODS

#### Materials

The following materials were used as received: Hydroxypropylmethylcellulose (HPMC K4M 4000 cps, pharmaceutical grade) was obtained from two different supply sources, A and B.

Polyvinyl pyrrolidone (PVP K-30, pharmaceutical grade) was obtained from the same two different supply sources of HPMC (A and B) and were donated by Amipharma Laboratories Ltd. (Sudan) and Citypharm Pharmaceutical Industries (Sudan), respectively.

Magnesium stearate (Mg stearate) was a product of Huzhou Zhanwang Pharmaceutical Co., Ltd. (China) and was donated by Shanghai-Sudan Pharmaceutical Co., Ltd. (Sudan).

Model drugs used in this study (Chlorpheniramine Maleate and Atenolol) were pharmaceutical grade products of Supriya Chemicals Pvt. Ltd and Ipca Laboratories Ltd (Mumbai, India), respectively, and were received as gift samples from Amipharma Laboratories Ltd. (Sudan). Other materials and reagents were analytical grade obtained from different commercial sources.

#### Experimental design

Fabrication of formulations and screening within this study were conducted following 2<sup>3</sup> full factorial screening design (Table 1) where three variables, namely, supply source of HPMC, supply source of PVP k-30 and drug solubility were each examined at two possible levels to determine their effects on the physical performance of produced matrices through 8 experimental runs as presented in Table 1.

### Preparation of matrices

For all runs, the drug: polymer (as matrixing agent) ratio is kept 1:1 where matrixing agent in all formulations was 1:1 mixture of HPMC and PVP with Mg stearate content (as a lubricant) fixed as 1% w/w. For each formulation run, ingredients for 200 tablets were weighed (Sartorius®, AG CP 124S, Germany), mixed separately using mortar and pestle for 10 minutes, lubricated and then compressed into tablets using a single punch tableting machine (Cadmach®, Ahmedabad, India) equipped with size 9 mm flat punch to produce matrix tablets with average weight of 202 mg and contain 100mg of loaded drug per unit dosage. The cleaning of the machine is carried out after preparation of each formulation run using ethanol. Each formulation run was separately packed in tightly closed glass bottle, labeled with the number of the run and evaluated for different attributes.

### Evaluation of matrix tablets

Produced matrix tablets within all batches run were subjected to the following assessment:

#### Friability test

Tablets within all runs were subjected to the official friability testing of Ph. Eur [10] where a total of 20 tablets from each produced tablets batch were weighed and placed in the drum of tablet friability tester (Erweka, Germany). The device was turned on at 25 round/min speed for 4 minutes. After dust removal, tablets were weighed and the friability was calculated using the average % loss from the two drums.

#### Hardness test

The test was conducted as per Ph. Eur. [10] in which 10 tablets from each formulation runs were placed in hardness tester (Erweka GmbH, Hensentamm, Germany). The device measures hardness in Newton (N) and diameter in millimeter (mm). The measured values and statistics of these values were calculated and recorded automatically by computer program connected to the device.

#### Dissolution test

Official BP dissolution method described in the general monograph of dissolution testing of oral dosage forms was followed for dissolution testing of Atenolol and Chlorpheniramine maleate tablets [10]. The dissolution test was carried out using basket apparatus (Erweka, Germany) set at 100 rpm. Dissolution medium

was 900 ml of 0.1M HCl (pH 1.2) at  $37 \pm 0.5^\circ\text{C}$  and 6 tablets from each batch were subjected to the test. Dissolution samples were withdrawn at predetermined time points, filtered and analyzed spectrophotometrically (double beam spectrophotometer, UV-1800, Shimadzu, Japan) either at 275 nm (for Atenolol) or 265 nm (for Chlorpheniramine Maleate) according to the BP specific monograph of each of the two drug product [11] considering sample taken at zero time as a blank sample.

For each drug, concentration in dissolution samples was determined by refereeing to state values of absorbance of 1% solution (in 0.1M HCl) of reference standards of the respective drugs measured in 1 cm length cube at the same wave length. The mean cumulative percentage of drug dissolved with respect to time was then generated for all tablet matrices.

#### Drug release kinetics

Dissolution data were subjected to model fitting and statistical analysis in order to explore the kinetics of the drug release. The model selected was power law [12] where dissolution data equivalent to < 60% drug release were fitted to the model to determine the diffusion exponent ( $n$ ) which characterizes drug release mechanism.

#### Statistical data analysis

Values of investigated matrix properties were presented as mean  $\pm$  SD (standard deviation). Inferential statistics relying on regression analysis and analysis of variance (ANOVA) followed by post-hoc Least Significant Difference test with a statistical significance level set at  $p < 0.05$  at 95% confidence limit (CI) were used to examine the individual and mutual effects of investigated factors on different attributes of matrix tablets. Comparison between drug release profiles of Atenolol and chlorpheniramine maleate containing matrices was made using independent t'test with  $p < 0.05$  considered statistically significant difference. Pearson correlation coefficient ( $r$ ) was used to evaluate the fitting strength of dissolution data to the power law model during determination of diffusion exponent of the drug release. Computations were aided by software computer package STATISTICA 10 (Statsofts Inc., USA)

### RESULTS AND DISCUSSION

Table 1 summarizes formulation and processing components for different matrix formulations in the screening design whereas properties of investigated matrices are summarized in Table 2.

**Table 1: Composition and ingredients source for different matrix formulations**

Batch No	Drug per tablet	HPMC % content and (source) <sup>a</sup>	PVP % content and (source) <sup>a</sup>	Drug type <sup>b</sup>	Mg st. (% w/w)
F1	100 mg	24.75 (B)	24.75 (B)	ATN	1%
F2	100 ~	24.75 (A)	24.75 (B)	ATN	1%
F3	100 ~	24.75 (B)	24.75 (A)	ATN	1%
F4	100 ~	24.75 (A)	24.75 (A)	ATN	1%
F5	100 ~	24.75 (B)	24.75 (B)	CPM	1%
F6	100 ~	24.75 (A)	24.75 (B)	CPM	1%
F7	100 ~	24.75 (B)	24.75 (A)	CPM	1%
F8	100 ~	24.75 (A)	24.75 (A)	CPM	1%

<sup>a</sup>A and B stands for the two different supply sources of both HPMC and PVP

<sup>b</sup>ATN and CPM stand for the drugs Atenolol and Chlorpheniramine maleate, respectively.

**Table 2: Properties of different matrix formulations**

Batch	Friability (%)	Hardness (N)	DE <sub>2 hrs</sub>	n*
F1	0.12 $\pm$ 0.10	79 $\pm$ 2	0.26 $\pm$ 0.03	0.507 $\pm$ 0.033
F2	0.02 $\pm$ 0.01	78 $\pm$ 9	0.28 $\pm$ 0.02	0.459 $\pm$ 0.008
F3	0.05 $\pm$ 0.02	74 $\pm$ 9	0.28 $\pm$ 0.03	0.496 $\pm$ 0.101
F4	0.17 $\pm$ 0.04	76 $\pm$ 2	0.26 $\pm$ 0.01	0.501 $\pm$ 0.191
F5	0.20 $\pm$ 0.07	72 $\pm$ 5	0.59 $\pm$ 0.05	0.697 $\pm$ 0.095
F6	0.35 $\pm$ 0.09	68 $\pm$ 2	0.73 $\pm$ 0.04	0.701 $\pm$ 0.084
F7	0.05 $\pm$ 0.03	83 $\pm$ 2	0.77 $\pm$ 0.06	0.658 $\pm$ 0.119
F8	0.05 $\pm$ 0.01	79 $\pm$ 5	0.67 $\pm$ 0.04	0.676 $\pm$ 0.049

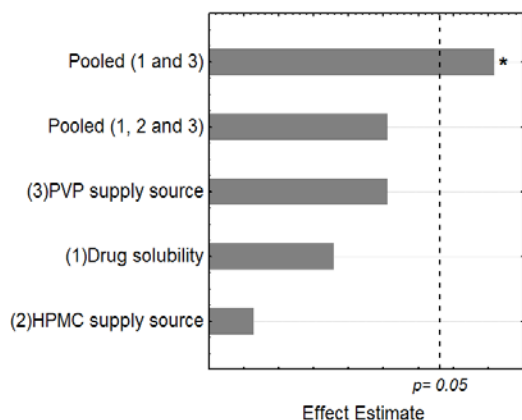
Values were presented as mean  $\pm$  respective standard deviation.\* Diffusion exponent of the drug release.

### Individual and combined influences of factors on matrix properties

Based on the displayed properties of different matrices (Table 2), it might be obvious that drug solubility, supply source of HPMC and/or PVP revealed dissimilar effects on properties of matrices and, therefore, discussion will be based on the influences on these properties.

### Influence of factors on friability and hardness properties

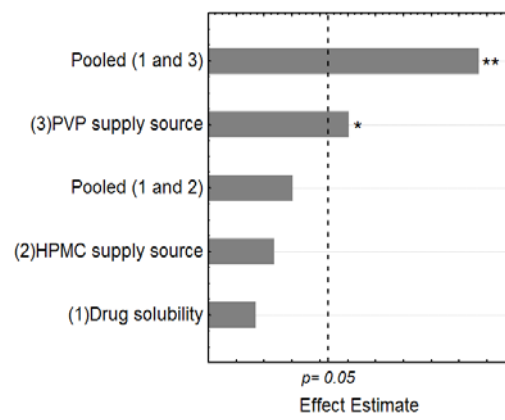
Displayed friability and hardness for different matrices were ranged 0.02-0.45% and 68-83N, respectively (Table 2). Although CPM



(A)

containing matrix formulations that incorporated PVP from source B (F5 and F6) showed higher friability values compared to other batches, all matrices were within the acceptable pharmacoepial limit for friability (< 1%) of uncoated tablets [10].

Effect estimate charts for the investigated factors (Figure 1A,B) showed that the interactive setting of PVP supply source and drug solubility has considerable effects on matrix friability and hardness. Moreover, PVP supply source proved to affect only the matrix hardness. Furthermore, both friability and hardness were shown to be less affected by HPMC supply source.



(B)

**Fig. 1: Absolute estimate of individual and pooled factors' effects on (A) friability and (B) hardness properties of produced matrix tablets with \* and \*\* indicating significant effect at  $p < 0.05$  and  $p < 0.01$ , respectively.**

Generally, tablet friability is a property that mostly related to the binder system utilized. PVP k-30 is known to possess binding strength that permits its application as a binder in addition to its function as a drug release modifier and, therefore, variation in supply source of PVP might be expected to affect both friability and hardness properties, as the result implies. The demonstrated variation in matrix hardness as a consequence of utilizing PVP of different supply sources might be attributed to the varied deformation properties that the two PVP might possess.

### Influences of factors on drug release characteristics

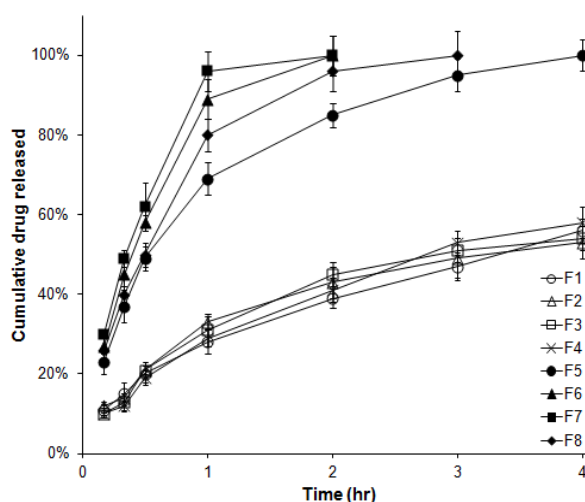
Release profiles of ATN and CPM from their respective matrices are shown in Figure 2. It is clear from the figure that matrices including the water soluble drug CPM (F5-F8) revealed higher cumulative drug release, at all time intervals of the dissolution study, as compared to those containing the water insoluble drug ATN (F1-F4). Moreover, all of CPM containing matrices (F5-F8) released the loaded drug after 4 hrs whereas those with ATN (F1-F4) achieved only 50-60% drug release at that time.

These findings encourage the assumption that drug solubility plays a major rule in drug release profile of these matrices which is in agree with relevant published works concerning the influence of drug solubility on the drug release from glyceryl monooleate matrix [13], polyethylene glycol [14] and HPMC based matrix [15].

It is presumed that influences of many factors on drug release from matrices would be more prominent during the initial phase of the drug release process where the rates at which the matrixing agent uptakes fluid and swells to form the gel layer are the determining processes for the drug release. Accordingly, dissolution efficiency of the drug at 2hr ( $DE_{2hr}$ ) was determined for all matrices from the corresponding dissolution data and used to explore the possible effects of investigated factors on the drug release property.

Displayed values of  $DE_{2hr}$  for different matrix batches were ranged 0.26-0.77 (Table 2) and the calculated average values of  $DE_{2hr}$  for

ATN and CPM containing matrices (0.27 and 0.69, respectively) were demonstrated to be significantly varied ( $p = 0.0001$  at 95% CI).



**Fig. 2: Drug release profiles of ATN containing matrices (F1-F4) and CPM including matrices (F5-F8).**

Regarding drug release kinetics, exhibited values for diffusion exponent of the drug release ( $n$ ) for different matrix batches were ranged 0.459-0.701 (Table 2). The mean values of the diffusion exponent of drug release calculated for ATN and CPM containing matrices (0.491 and 0.683, respectively) were computed to be considerably different ( $p = 0.00003$  at 95% CI).

In swellable matrix tablets, the dynamics of gel layer thickness determine the drug release kinetics. Participation of drug diffusion,

polymer chain relaxation and matrix erosion to drug release in HPMC matrices is recognized to produce  $n$  values that range from 0.45 to 1.0 [16].

Although contribution of more than one mechanism in the release of sparingly soluble drugs from matrix tablets is well documented in the literature [17, 18], demonstrated values for  $n$  with ATN containing matrices support the fickian mechanism in which drug diffusion is expected to control the release process. With CPM matrices, however, anomalous mechanism is evident where both drug diffusion and polymer chain relaxation are expected to control the drug release. Findings related to drug release of CPM containing matrices are in accord with the conclusion of relevant published work on release kinetics of verapamil-HCl from HPMC matrices [19].

Exhibited values of correlation coefficients associated with fitting of ATN and CPM release data to the power law model were ranged

0.9903-0.9998 ( $p < 0.05$ ) for all matrix formulations, indicating suitability of selected model for determination of diffusion exponent,  $n$ , of the loaded drugs.

Among the three factors investigated for their possible impacts on drug release properties, only drug solubility was found to have a considerable influence on both  $DE_{2 \text{ hrs}}$  and diffusion exponent ( $n$ ) characteristics of the drug release from different matrices ( $p < 0.01$  at 95% CI for its effect on both properties, Figure 3A,B).

The observed influence of drug solubility on  $DE_{2 \text{ hrs}}$  and  $n$  characteristics could be attributed to the nature of both drugs. With water soluble drug (CPM), the enhanced dissolution and release of the drug before formation of an effective polymeric gel that hinders the drug release would result in accelerated drug release with no (or a little) contribution of the gel characteristics on the release kinetics, especially during the initial phase of the release.

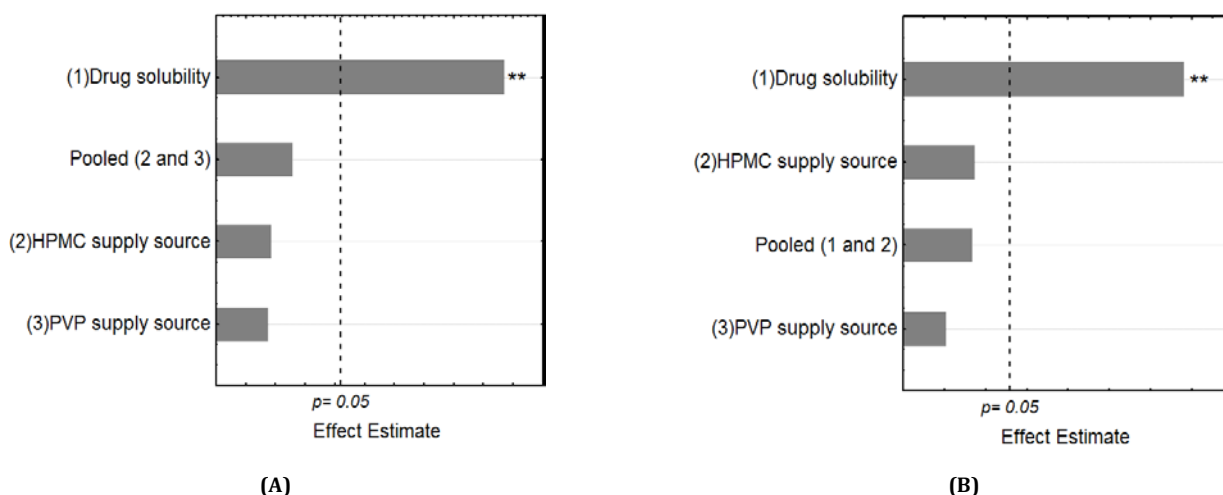


Fig. 3: Absolute estimate of individual and pooled factors' effects on (A)  $DE_{2 \text{ hrs}}$  and (B) diffusion exponent characteristics of drug release of different matrices with \*\* indicating significant effect at  $p < 0.01$ .

On the contrary, the reduced chance for the water insoluble drug (ATN) to escape the gel barrier, due to the expected slow dissolution rate of the drug, would provide a situation of a comparative low drug release and involvement of polymeric gel to share a role in the kinetics of the drug release process.

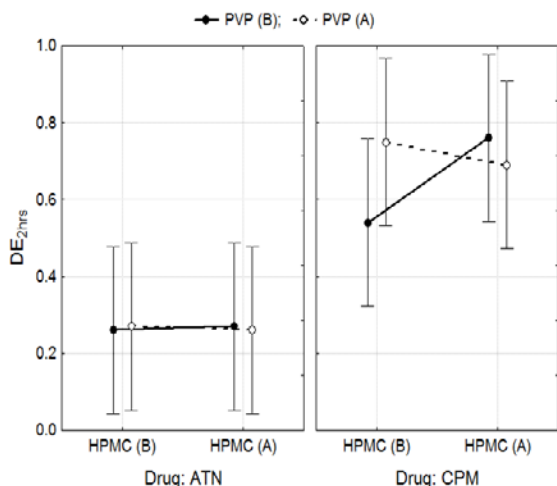


Fig. 4: Marginal Means  $\pm$  SE for  $DE_{2 \text{ hrs}}$  of Atenolol (ATN) and Chlorpheniramine maleate (CPM) released from different matrices as related to variation of HPMC and PVP supply sources (A and B, for each).

It might be obvious from Figure 4 A,B that matrix formulations including ATN were not affected by supply source of PVP or HPMC. However, with matrices incorporating CPM, formulation containing HPMC and PVP, both of source B (F5) revealed smaller value of  $DE_{2 \text{ hrs}}$  (0.54, Table 2) as compared to that composed of PVP of source B and HPMC of source A (F6), which measured  $DE_{2 \text{ hrs}}$  of 0.76 (Table 2). The inverse is also valid for matrices containing CPM and PVP of source A.

Nevertheless, the observed influences of supply source of PVP and/or HPMC on drug release of CPM containing matrices might not be substantial enough for statistical consideration (Figure 3 A,B)

**CONCLUSION**

PVP supply source was verified to influence matrix hardness whereas the combined influence of PVP supply source and drug solubility proved to affect both matrix friability and hardness properties. Moreover, drug solubility demonstrated to influence dissolution efficiency and release kinetics properties of the prepared matrices. None of the investigated matrices' properties appears to be affected by the supply source of HPMC, at least under the present study conditions.

**CONFLICT OF INTERESTS**

Declared None

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