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Adsorption of Acidic and Basic Drugs by Cereal Brans

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Studies on the adsorption of three acidic and three basic drugs on wheat bran and rice bran have been reported. Rice bran was found to be a better adsorbent than wheat bran. Basic drugs were adsorbed to a much larger extent compare to acidic drugs. Amongst acidic drugs adsorption of paracetamol was highest. Amongst basic drugs adsorption of promethazine was lowest. Data obeyed Freundlich adsorption isotherm. Acid/base treatment increased the adsorption capacity of bran but the increase was more for wheat bran than rice bran. The possible application of adsorption data in pharmacy has been explored. For the basic antipsychotic drugs, rice bran was found to be a good adsorbent and thus can be effectively used as a safe antidote with no side effects.

Although charcoal is considered to be a useful pharmaceutical adsorbent[1-2] and universal antidote[3] because of its high adsorption capacity, it suffers from several serious disadvantages[4]. For example, activated charcoal, being a very strong adsorbent, adsorbs nutrients and enzymes along with poisons. Activated charcoal gives embolising particles likely to cause obstruction of arteries by forming clots. Activated charcoal also leads to removal of blood platelets. Moreover, highly ionized substances of low molecular weight and drugs that are poorly soluble in acidic media are not well adsorbed. Furthermore, charcoal is a foreign matter, difficult to be adminisered in powdered form to an un-cooperative patient and charcoal tablets are half as effective as powdered material.

Dietary fibre, on the other hand, is easy to administer since it is a food supplement. It is not digested or absorbed into the body and has no harmful effects. Perusal of the literature shows that cereal bran, a kind of dietary fibre, has the potential to be used as an adsorbent. Adsorption of dyes, metal ions and pesticides by cereal bran has been reported by a number of workers[5-7]. Adsorption of bile acids and carcinogens by cereal bran has also been studied[8-9]. However, most of the studies emphasize the importance of fibre in food. The role of isolated cereal bran as a pharmaceutical adsorbent has not received much attention so far. In the present paper, an attempt has been made to explore the possibility of using wheat and rice brans as adsorbent materials, using three acidic and three basic drugs.

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MATERIALS AND METHODS

Metronidazole, tinidazole, paracetamol, chlorpromazine hydrochloride, promethazine hydrochloride and triflupromazine hydrochloride were obtained from various manufacturers. Dimethyl formamide (DMF) (Qualigens Fine Chemicals) was dried by keeping in contact with Linde type 4A molecular sieves and purified by distillation under reduced pressure. Wheat bran, a by-product of wheat milling industry and rice bran, a by-product of rice milling industry, were obtained locally.

Wheat and rice brans were washed repeatedly with water till the supernatant was clear. Acid-treated bran was prepared by shaking 10 g of bran with 50 ml of 1 N HCl for 24 h followed by washing with distilled water till the washings were free of chloride ions. Base-treated bran was prepared in a similar manner using 0.5 N KOH. The base-treated bran was washed with water till the washings were neutral. The simple bran as well as the acid/base-treated washed bran

was rinsed with 95.6% ethanol and dried in air oven at 100°. Dried bran was passed through sieves and 50-60 mesh sample was collected and used.

Adsorption of drugs by bran:

Drug concentration was varied from 0.5 to 10 mM in each case. Solvent was 10% DMF in the case of acidic drugs and water in the case of basic drugs. Two hundred mg portions of bran, taken in stoppered glass tubes, was mixed with 10 ml of drug solution of different concentrations, varying from 0.5 to 10 mM. Blank sets without bran and reference sample without drug were prepared in the same manner. Preliminary experiments showed that a time period of 24 h was sufficient for attainment of equilibrium. The tubes were shaken at 25° for 24 h after which the bran was filtered and the filtrate was analyzed for drug concentration using ultraviolet absorption spectroscopy. Adsorption spectra of drug solutions in the experimental and blank sets were measured in the wavelength range 200-500 nm after appropriate dilution against a reference. Extinction coefficients, determined from the known concentrations of the blank set, were used to determine the concentration of drug at equilibrium. The amount of drug adsorbed by bran was calculated as: x/m (mg/g) = $10(c_i - c_e)MW/1000$ m, where x/m is the amount (mg) of drug adsorbed per g of bran, c_i and c_e are the initial and equilibrium concentrations of the drug, respectively, m is the weight of bran and factor 10 is the volume of drug solution taken for adsorption.

RESULTS AND DISCUSSION

The wavelength corresponding to absorption maxima (λ_{max}) and the molar extinction coefficients (ε) for various drugs are given in Table 1. The adsorption isotherms, obtained by plotting x/m values for various drugs against equilibrium concentration of drug (c_e) at 25°, are shown in figs. 1 and 2 for some of the samples. It is observed that the amount adsorbed increased with increase in the concentration of drug in each case. However, the shape of the adsorption isotherm is not simple monomolecular (Type I) in most cases. The maximum weights of various drugs adsorbed per g bran are given in Table 2.

The results show that, in general, rice bran is a better adsorbent than wheat bran. Basic drugs are adsorbed to a much larger extent than acidic drugs. Amongst acidic drugs, adsorption of paracetamol is much higher than other drugs. Amongst basic drugs, the order of adsorption was chlorpromazine hydrochloride>triflupromazine hydrochloride> promethazine hydrochloride. It was thought of interest to correlate the adsorptive capacity of various drugs to the polarity of drug molecules. For this purpose the polar surface area of various drugs was calculated using software molinspiration[10]. The values for various drugs are given in Table 1. It is seen that the polarity of basic drugs is much lower than that of the acidic drugs and amongst acidic drugs paracetamol is least polar. Reference to Table 2 shows that the extent of adsorption of various drugs varies inversely as the polar surface area of drugs. It can, therefore, be concluded that the bran surface is predominantly hydrophobic in nature and the extent of adsorption is directly proportional to the hydrophobicity of the drug. The three basic drugs used have same structure except the substituent at position 2 of the tricyclic ring. Thus the polar surface area is same for all drugs. The electron-withdrawing -Cl and $-CF_3$ groups in chlorpromazine hydrochloride and triflupromazine hydrochloride, however, increase the positive charge at the

TABLE 1: SPECTROPHOTOMETRIC AND PHYSICO-CHEMICAL PARAMETERS OF VARIOUS DRUGS.

Drug*	λ_{max} (nm)	ε ($M^{-1}cm^{-1}$)	Polar Surface Area	pKa	Log P
Metronidazole	318	9320	83.9	2.60	-0.35
Tinidazole	317	9120	89.9	-	0.58
Paracetamol	248	11131	49.3	9.90	1.36
Chlorpromazine HCl	306	4558	10.9	9.30	5.10
Triflupromazine HCl	305	3453	10.9	9.20	5.17
Promethazine HCl	299	3640	10.9	9.10	4.51

* The solvent was 10% DMF in the case of metronidazole, tinidazole and paracetamol and water in the case of chlorpromazine HCl, triflupromazine HCl and promethazine HCl. Polar Surface Area has been calculated using software molinspiration[9]. pKa and log P values are taken from literature[10-12].

TABLE 2: MAXIMUM AMOUNT ADSORBED AND BRAN REQUIRED PER DOSE FOR VARIOUS DRUGS.

Drug	Bran	X/m (mg/g)	Dose (mg)	Bran required/dose (g)
Acidic drugs				
Metronidazole	Wheat Bran	15.7	200	13.2
	Wheat Bran KOH	16.9	200	11.9
	Wheat Bran HCl	19.8	200	10.1
	Rice Bran	32.1	200	6.2
	Rice Bran-KOH	41.7	200	4.8
	Rice Bran-HCl	42.5	200	4.7
Tinidazole	Wheat Bran	16.5	500	30.3
	Rice Bran	32.4	500	15.4
Paracetamol	Wheat Bran	33.0	500	15.2
	Rice Bran	58.4	500	8.57
Basic Drugs				
Chlorpromazine HCl	Rice Bran	148.8	25	0.17
Triflupromazine HCl	Rice Bran	128.1	25	0.20
Promethazine HCl	Rice Bran	111.3	25	0.22

The most commonly used doses for various drugs are mentioned in column 4.

basic nitrogen atom. Since these drugs are adsorbed to a larger extent as compared to promethazine, it appears that the bran surface has some anionic sites as well which play a role in the adsorption of basic drugs. Further, octanol-water partition coefficient (logP) and ionization constant (pK_a) are also commonly used measures of the hydrophobic and ionic nature of drugs, respectively. Higher the log P value, the more hydrophobic is the drug. The lower the PK_a value, the more ionic is the drug. log P and pK_a values of the acidic and basic drugs used, taken from literature[10-12] are given in Table 1. It is seen that the values are much higher for paracetamol than other acidic drugs and are lower for prometbazine than other basic drugs. This gives further

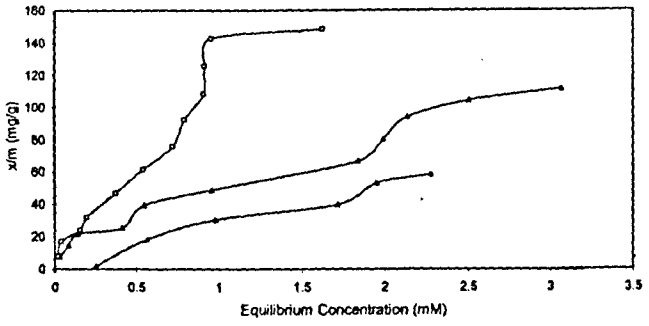

Fig. 1: Adsorption of various drugs by rice bran.

x/m is the milligrams of promethazine (-△-), chlorpromazine (-□-) and paracetamol (-▲-) adsorbed per gram bran.

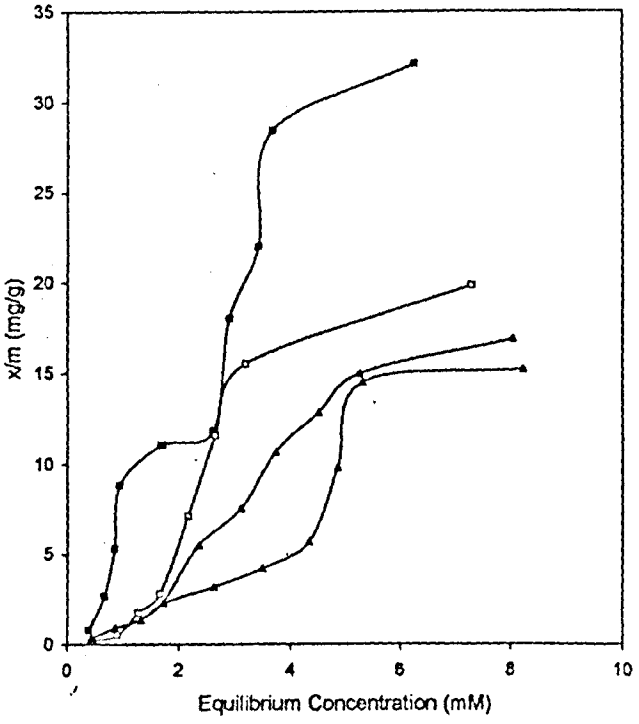

Fig. 2: Adsorption of metronidazole by wheat bran and rice bran.

x/m is the milligrams of metronidazole adsorbed per gram wheat bran (-▲-), rice bran (-■-), acid-treated wheat bran (-□-) and base-treated wheat bran (-△-).

support to the above-mentioned conclusions.

Langmuir adsorption isotherm equation was not applicable. The data was, therefore, analysed using Freundlich adsorption isotherm, $x/m=Kc^{1/n}$. Langmuir adsorption isotherm assumes that the adsorbent surface is homogeneous and heat of adsorption is independent of surface coverage. Freundlich adsorption isotherm, on the other hand, assumes a logarithmic fall in heat of adsorption with surface coverage due to surface heterogeneity and adsorbate-adsorbate interactions[13]. Moreover, the Freundlich equation is generally valid at low surface coverages. Thus the bran surface is heterogeneous with respect to adsorption of these drugs. The log x/m versus log C_e plots, shown in fig. 3 for some of the systems, were used to calculate the two parameters, K and 1/n of the Freundlich adsorption isotherm. K and 1/n values for the various systems studied, are given in Table 3. Constant K is related to the energy of adsorption and is a measure of the adsorptive capacity of the adsorbent for the particular adsorbate under examination and 1/n is a dimensionless parameter, related to the intensity of drug adsorption[4]. Abe *et al.*[2] while studying the adsorption of local anesthetics onto carbon, have shown that the parameter 1/n is inversely related to the affinity of drug to adsorbent. In the present systems, it is seen that K and 1/n values depend on the nature of bran and nature of drug. In general, K values are higher and 1/n values are lower for rice bran and basic drugs as compared to wheat bran and acidic drugs, respectively.

It was thought of interest to treat wheat and rice bran

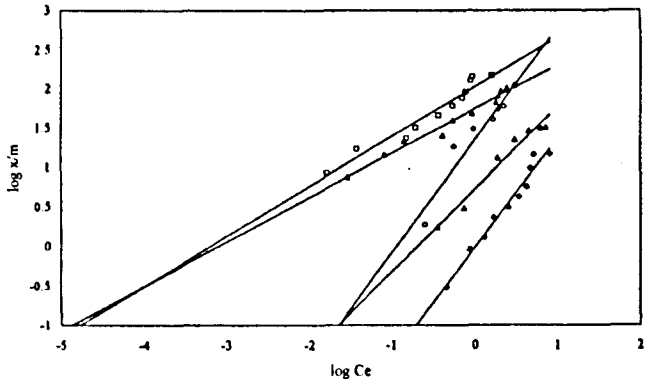

Fig. 3: Log x/m versus log c_e plots for various drugs.

x/m is the milligrams of metronidazole (-◆-) adsorbed per gram wheat bran and chlorpromazine (-□-), tinidazole (-▲-), paracetamol (-○-), promethazine (-△-) adsorbed per gram rice bran and c_e is the equilibrium drug concentration.

with acid and base, so as to increase the porosity of bran surface and thus improve its adsorptive capacity. Acid-treated and base-treated brans were used as adsorbent for one of the drugs, metronidazole, keeping all other conditions same as for untreated bran. The results for wheat bran are shown in fig. 2. The maximum adsorptive capacity for the adsorption of metronidazole by treated wheat and rice bran is shown in Table 2. It was found that the adsorptive capacity of bran increased both on acid and base treatment, but the increase was relatively more in the case of rice bran than wheat bran. The order of the extent of adsorption was acid-treated bran>base-treated bran>simple bran.

An attempt has been made to explore the possible pharmaceutical applications of the adsorption results discussed above. The data in Table 2 show that acidic drugs require higher doses and they have low adsorption capacity. Thus the weight of bran required per dose is very high (~ 4 to 30 g). Bran is, therefore, not a very useful adsorbent for these drugs. Basic drugs, on the other hand, require much smaller doses and their adsorption capacity is also high. Thus very small quantity of bran (~ 0.2 g) is required per dose. Hence for these drugs, bran is an excellent adsorbent and can be effectively used as a safe antidote with no side effects. The toxicity of antipsychotic and antidepressant drugs due to overdose or accidental intake is commonly encountered[14]. Thus control of toxicity of these drugs is an important is-

TABLE 3: FREUNDLICH ADSORPTION ISOTHERM PARAMETERS FOR VARIOUS SYSTEMS.

Drug	Bran	1/n	K
Metronidazole	Wheat Bran	1.32	0.95
	Rice Bran	1.02	5.97
Tinidazole	Wheat Bran	1.12	1.54
	Rice Bran	1.05	5.24
Paracetamol	Wheat Bran	1.05	12.4
	Rice Bran	1.43	22.2
Chlorpromazine HCl	Rice Bran	0.63	105.7
Triflupromazine HCl	Rice Bran	0.48	59.2
Promethazine HCl	Rice Bran	0.56	54.8

The Freundlich adsorption isotherm parameters were calculated from log x/m versus log c_e plots for various systems. x/m has been expressed in mg/g and c_e in mM units.

sue. The present work, therefore, leads to an important conclusion that rice bran has the potential to be used as a safe and effective pharmaceutical adsorbent for antipsychotic and antidepressant drugs

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