Formulation and evaluation of Psyllium Husk-containing granules as a carrier to sustain the release of Water-Soluble drugs II: Mechanism of Drug Release

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Abstract:In previous work, the use of psyllium huskas the main component of sustained release preparations, was investigated. Granules of Metformin HCl containing different hydrocolloids namely; psyllium Husk and sodium carboxy-methyl cellulose (Na CMC), "System I", and granules of sodium salicylate containing these hydrocolloids in addition to stearic acid, "System II' were prepared. In vitro release studies in phosphate buffer solution (pH 6.8) clearly revealed the superiority of psyllium husk and Na CMCcombination in sustaining the release of both drugs. The introduction of stearic acid in formulations SC5 and SP5 have, significantly, slowed down the release of Sodium salicylate to 46% and 53%, respectively, after 7 hours. Mathematical modeling of the release data revealed that the release mechanism which describes the diffusion of both drugs from these systems is driven by a complex behavior such as swelling, matrix erosion as well as diffusion through the swollen matrix of most formulations. Evaluation of the drug release mechanism from these systems suggested that the release could be described by a complex mechanism, which may involve First-order kinetics, Higuchi diffusion controlled as well as Korsmeyer Peppas models.

Keywords: Release mechanism, granules, metformin, Psyllium husk, stearic acid

Introduction

The purpose of this paper is to investigate the mechanism by which the drug is released from granules formulated earlier in our laboratories (1). Mathematical models that describe the drug release from such formulations, significantly clarify the mechanisms by which drugs are released from different systems in addition to providing more general guidelines for the development of other systems. In our study,

the release data are fitted to first order, Higuchi and korsmeyer exponential equations.First order kinetics model: the release of the drug which follows first order kinetics can be expressed by the equation: Ln (100-Q) = ln (Q_0)-k_1t. This relationship can be used to describe the drug dissolution from pharmaceutical dosage forms such as those containing water-soluble drugs in porous matrices.Higuchi model: In 1963, T. Higuchi proposed this model to describe the drug release from matrix system, and found out that the amount released is directly proportional to the square root of time (2).

Higuchi model is based on the hypothesis that:Initial drug concentration in the matrix is much higher than drug solubility.Drug diffusion takes place only in one dimension (edge effect must be negligible).Drug particles are much smaller than system thickness.Matrix swelling and dissolution are negligible. As well as, drug diffusivity is constant and perfect sink conditions are always attained in the release environment. Higuchi model is given by the equation:

$Q = k H t^{1/2}$, where (kH) is Higuchi dissolution constant, obtained from the percentage of the drug released against square root of time plot. Q= percentage drug released at a time (t).This model can be used to describe the drug dissolution from several modified release dosage forms such as matrix systems containing water soluble drugs.Korsmeyer-Peppas model (the power low) A simple relationship which described the drug release from polymeric systems, was derived by korsmeyer et al in 1981 (3). To investigate the mechanism of drug release from such systems, first 60% drug release data were fitted in korsmeyer-peppas model:Log [F] = n Log [t] + Log [Kp], Kp = release rate constant. The diffusion exponent (n) which is indicative of the mechanism of drug release, was obtained by plotting the log value of percent drug released (F) against log time (t) for each formulation.(n) value of 0.45 indicates Fickian (case I) release, n>0.45 but <0.89 is non-Fickian (anomalous) release, and>0.89 indicate super case II type of release. Case II generally refers to the erosion of the polymeric chain and anomalous transport (non-Fickian) refers to a combination of both diffusion and erosion controlled drug release. This model has been used frequently to describe the drug release from several modified release dosage forms (4-6).

Materials and methods

Preparation of the granules: prepared as previously discussed in our laboratories (1)

Formulations (F1-F9) by wet granulation (Table 1):Accurately Weighed quantity required (50g formula) of Metformin Hcl, Chitosan, Psyllium husk, Na CMC and Lactose which is pre-sieved through 250µ sieve. The weighed items were mixed together for 15 minutes. Sufficient quantity of water was added gradually to form wet mass and mixed for 5minutes using mortar and pestle. The mixture was granulated using oscillating granulator. The granules were air dried at 55°C for 1hour then allowed to dry at room temperature. The granules were sieved through 1000 µ sieve and the agglomerates were broken and lubricated with Mg stearate and silicon dioxide. The granules were stored in a desiccator for future use. The required dose was filled in hard gelatin capsules before conducting the release studies.

Formulations (F10, F11, SC1-SC5, SP1-SP5): melting and congealing (Tables 2-4): Each ingredient in the formula was accurately weighed and sieved through 450µ sieve. The weighed metformine Hcl (F10, F11) or sodium salicylate (SC, SP) and the hydrophilic polymer (Psyllium husk, Na CMC) were suspended in the melted stearic acid and then allowed to congeal and solidify. The solid mass pressed through a 750 µ sieve. The granules were stored in a desiccator for future use. The required dose was filled in hard gelatin capsules before the release studies.

System I: Psyllium husk and Na CMC combinations as release retarding carriers.

Table 1: Composition of formulations (F1-F6)

	F1	**F2**	**F3**	**F4**	**F5**	**F6**
API+Excipients	% (w/w)	% (w/w)	% (w/w)	% (w/w)	% (w/w)	% (w/w)
Metformin Hcl	50	50	50	50	50	50
Psyllium husk	36	26	23	20	10	46
Na CMC	10	20	23	26	36	-
Lactose	3	3	3	3	3	3
Mg stearate	0.5	0.5	0.5	0.5	0.5	0.5
Silicon dioxide	0.5	0.5	0.5	0.5	0.5	0.5
Purified water	Qs					

Table 2: Composition of formulations (F10-F11)

	F10	**F11**
API+POLYMERS	Percent % (W/W)	Percent % (W/W)
Metformin Hcl	14.3	54.4
stearic acid	71.4	13
Na CMC	14.3	32.6

System II: Stearic acid and Na CMC as release retarding carriers in different ratios.

Table 3: Composition of formulations SC1-SC5

	SC1	SC2	SC3	SC4	SC5
API+POLYMERS	% (W/W)	% (W/W)	% (W/W)	% (W/W)	% (W/W)
Stearic acid	85	75	65	55	45
Na CMC	7.5	17.5	27.5	37.5	47.5
Sodium salicylate	7.5	7.5	7.5	7.5	7.5

Stearic acid and Psyllium husk as release retarding carriers in different ratios.

Table 4: Composition of formulations SP1-SP5

	SP1	SP2	SP3	SP4	SP5
API+POLYMERS	**%(W/W)**	**%(W/W)**	**%(W/W)**	**%(W/W)**	**%(W/W)**
stearic acid	85	75	65	55	45
Psyllium husk	7.5	17.5	27.5	37.5	47.5
Sodium salicylate	7.5	7.5	7.5	7.5	7.5

Statistical analysis:the percentage of drug released of each formulation were analyzed by the analysis of variance ANOVA. The P-values at (95% confidence level) were in the range of (0.001-.006) which is considered statistically very significant and the same test was carried out for formulations (F1-F11) for comparison of the difference in the percentage drug released at 4^{th} hour of release time, P-value was $\leq$ 0.05 which is statistically significant. The percentages of drug which have been released over 7 hrs, for formulations (SC1-SC5) and (SP1-SP5) were also were found to be significantly different, P- value ≤ 0.05.

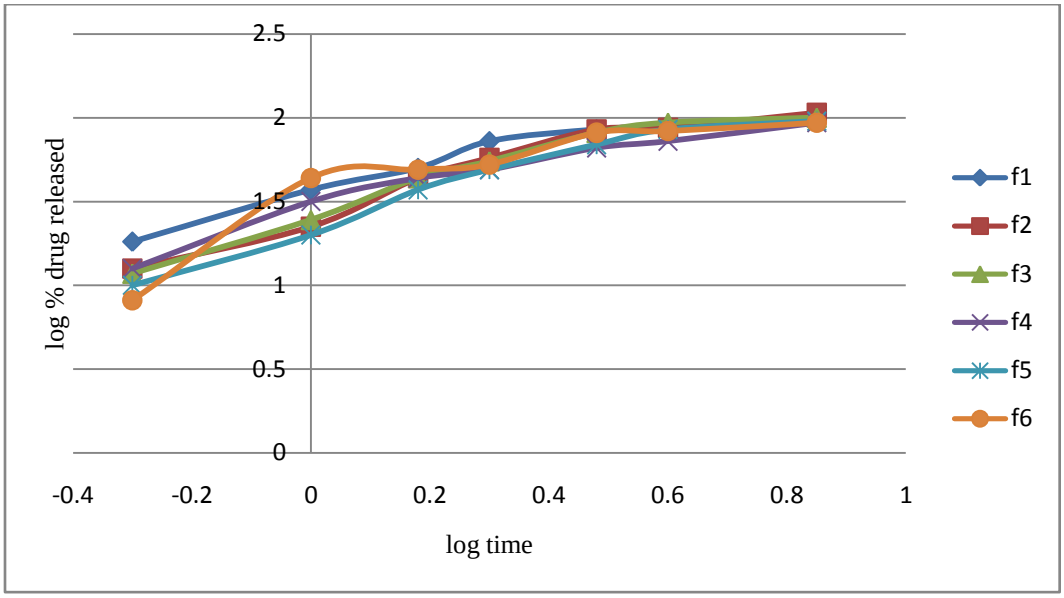
Results and discussion

Kinetic data analysis for formulations (F1-F6):Data in tables 5-7 and figures 1-7 concluded that mathematical modeling of the drug release data are best described by first – order kinetics with the highest R^2 compared to both Higuchi and Korsmeyer-peppas models. The n value > 0.45 indicate that the drug release is classified as non- Fickian (anomalous) diffusion controlled, and super case II release (swelling and relaxation of the polymer). This behavior is attributed to the high concentration of Na CMC in formulation 5.

Table 5: kinetic analysis data for formulations (F1 - F6)

First order equation			**Hiquchi equation**		**Korsmeyer-peppas equation**		
Formula code	**K**	**R^2**	**K□**	**R^2**	**K peppas**	**n**	**R^2**
F1	0.46	0.938	41.6	0.856	36.3	0.64	0.895
F2	0.55	0.982	52.6	0.943	26.3	0.86	0.938
F3	0.58	0.989	49.8	0.909	26.3	0.86	0.933
F4	0.39	0.986	40.9	0.976	27.5	0.73	0.934
F5	0.51	0.993	48.5	0.955	21.9	0.90	0.948
F6	0.40	0.954	42.2	0.873	26.9	0.84	0.879

Figure 1 : Korsmeyer-Peppas plots for formulations F1-F6



Kinetic data analysis for formulations SC1-SC5:Stearic acid and Na CMC as release retarding polymers in different ratios.These formulations also best characterized by first order model with the highest values of R^2 and n values indicate the non-Fickian (anomalous) diffusion mechanism of release.

Table 6: kinetic analysis data for formulations (SC1-SC5)

Formula code	1st order kinetics		Higuchi model		Korsmeyer-peppas		
	K1	R^2	KH	R^2	KP	n	R^2
SC1	0.16	0.953	29.8	0.945	22.9	0.58	0.950
SC2	0.17	0.954	29.7	0.932	23.4	0.55	0.907
SC3	0.14	0.975	27.0	0.980	23.4	0.57	0.980
SC4	0.11	0.997	24.2	0.992	16.9	0.61	0.990
SC5	0.08	0.984	20.5	0.984	12.0	0.70	0.965

Figure 2: First order plot for formulations (SC1-SC5)

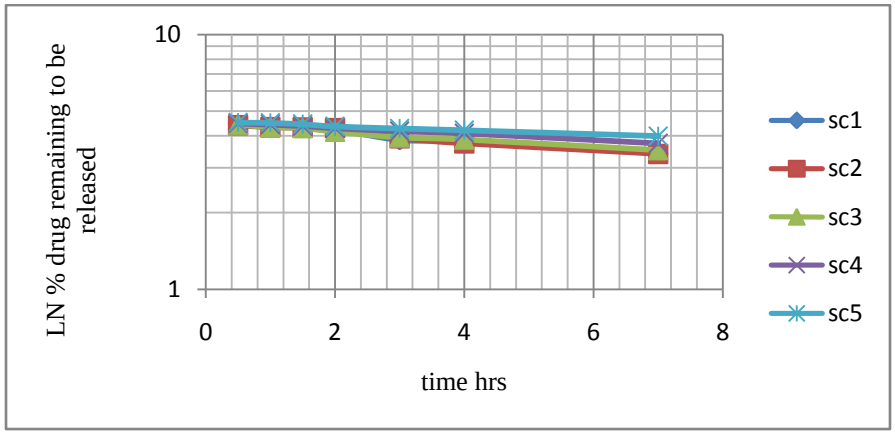


Figure 3: Higuchi equation plot for formulations (SC1-SC5)

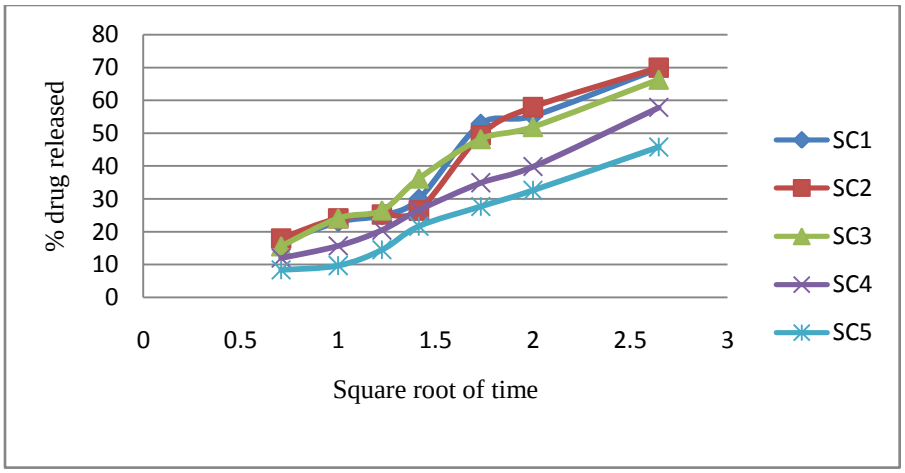
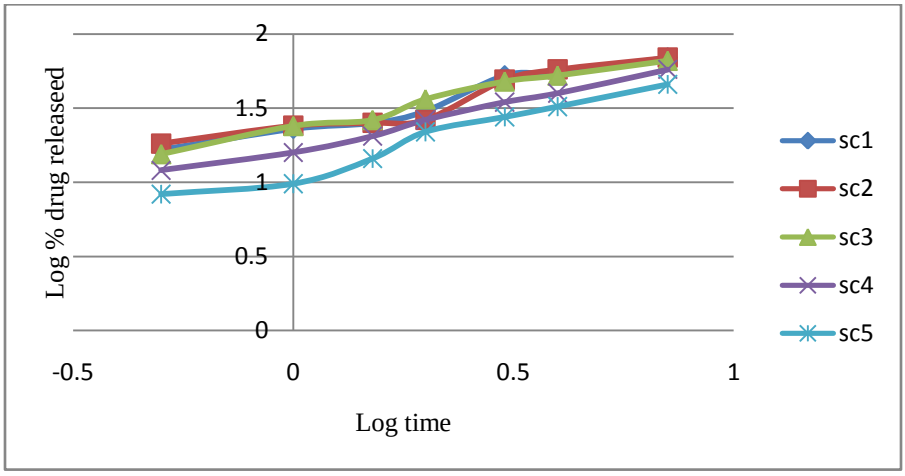


Figure 4: korsmeyer-peppas plot for formulations (SC1-SC5)



Stearic acid and Psyllium husk as release retarding polymers in different ratios: The above formulations were best characterized by Higuchi model. The release exponent, n values indicate the non-Fickian (anomalous) diffusion mechanism of release and SP5 by super case II release which is attributed to the higher content of Psyllium in the formulations.

Table 7: kinetic analysis data for formulations (SP1-SP5)

Formula code	1st order kinetics		Higuchi model		Korsmeyer-peppas		
	K1	R^2	KH	R^2	KP	n	R^2
SP1	0.21	0.914	35.6	0.900	23.4	0.76	0.902
SP2	0.19	0.994	34.8	0.991	15.5	0.89	0.971
SP3	0.14	0.925	29.6	0.956	15.1	0.83	0.958
SP4	0.11	0.862	26.5	0.925	13.8	0.88	0.878
SP5	0.11	0.856	26.8	0.922	12.9	0.92	0.911

Figure 5: First order plot for formulations (SP1-SP5)

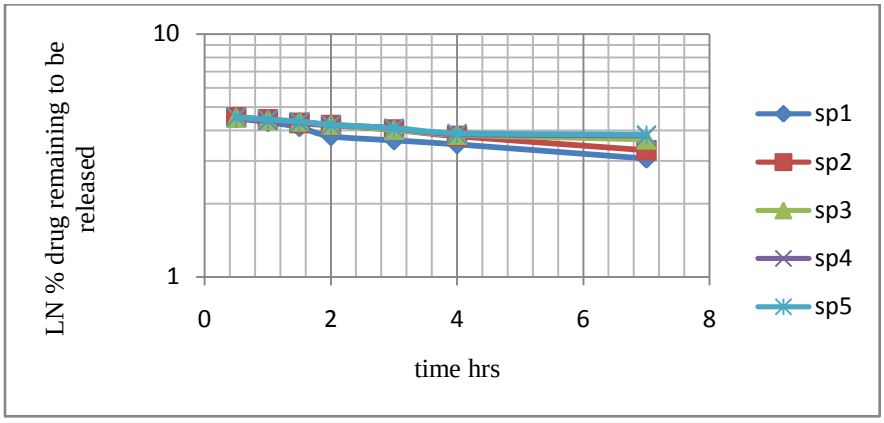


Figure 6: Higuchi equation plot for formulations (SP1-SP5)

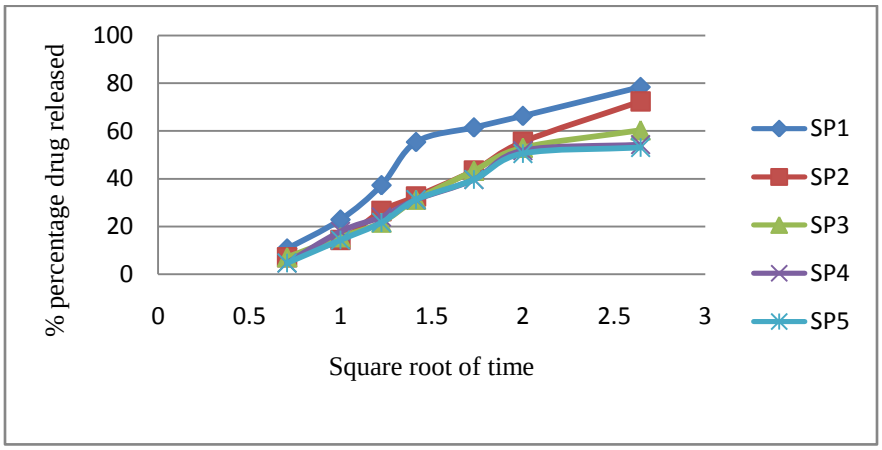
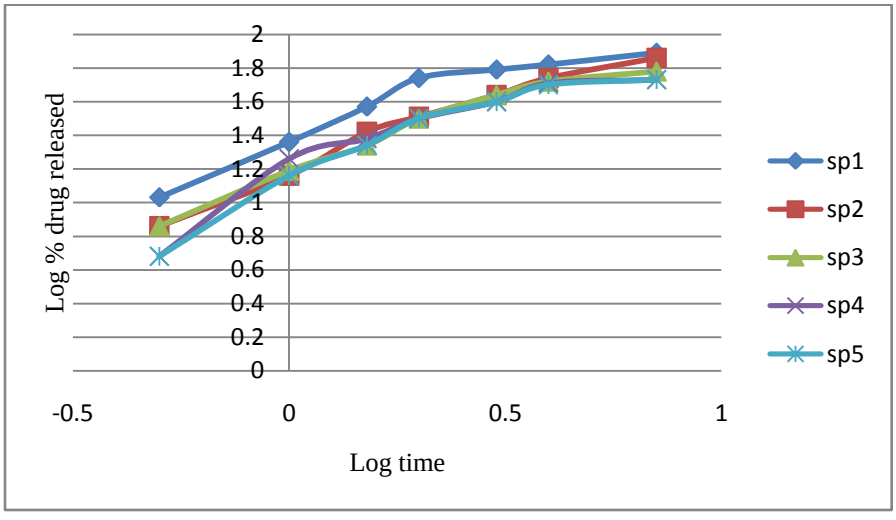


Figure 7: korsmeyer-peppas plot for formulations (SP1-SP5)



Therefore, drug release is driven by a complex mechanism, where swelling plus erosion of matrix and diffusion of drug through the swollen matrix take place simultaneously.

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