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FORMULATION AND EVALUATION OF PSYLLIUM HUSK-CONTAINING GRANULES AS A CARRIER TO SUSTAIN THE RELEASE OF WATER-SOLUBLE DRUGS I: CHARACTERIZATION AND RELEASE STUDIES

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ABSTRACT

This work describes many attempts to sustain the release of freely water-soluble drugs, namely Metformin HCl and sodium salicylate, which are used as model drugs. The large dose of Metformin HCl represents an additional obstacle to the formulation of an acceptable dosage form of this drug. The use of psyllium husk, as the main component of sustained release preparations, was investigated and reported in the literature with success (Yasir *et al.*, 2010). Granules of Metformin HCl containing different hydrocolloids such as 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. FTIR spectra revealed that these drugs were not affected by the formulation process. Physicochemical characterization of the formed granules has shown that the prepared granules were generally free flowing with good compressibility. In Vitro release studies revealed a significant decrease in the percentage of drug released, over 7 hours, as the percentage of Na CMC was increased in the formulations studied. A synergetic effect of combined Psyllium and Na CMC on sustaining the drug release was noticed. Psyllium was found to be unable to slow down the drug release alone, probably due to the long swelling time of this hydrocolloid.

KEYWORDS: Psyllium Husk, Metformin HCl, Sodium carboxy-methyl cellulose, Sodium salicylate, Sustained release.

INTRODUCTION

The demand for sustaining the release of freely water-soluble drugs has been growing for the last few decades. Extending the release of drugs with large doses from different dosage forms represents an additional challenge. Metformin HCl, which is an orally administered drug used to lower blood glucose levels in patients with non- insulin dependent diabetes mellitus, was chosen as a model drug, with a large dose. Sodium salicylate was chosen as a model drug with a small dose.

The primary drug release rate limiting ingredients of hydrophilic matrices are polymers that would swell when they come in contact with an aqueous solution and form a gel layer on the surface of the system. When the release medium is thermodynamically compatible with a polymer, the solvent penetrates into the free spaces between macromolecular chains. The polymer may undergo a relaxation process due to the stress of the penetrated solvent, so that the polymer chains become more flexible and the matrix swells. This allows the encapsulated drug to diffuse more rapidly to the bathing fluid. On the other hand, it would take more time for drug to diffuse out of the matrix since matrix swelling lengthens the diffusion path.

In order to extend the release of Metformin HCl a Hydrophilic matrix system **w**as adopted. This system is represented by a combination of the following.

(1) Psyllium seed husks which are portions of the seeds of the plant *Plantago ovata*. They are hygroscopic, which allows them to expand and become mucilaginous. Psyllium husk possesses good swelling and gelling properties and, therefore, when used as a matrix forming agent in the modified release formulation, it forms a swollen mass (swelling index is about 20 times in volume)**.** Psyllium husk are preferred over synthetic materials due to their safety, low cost, availability, high affinity for water, chemically inert & purely mechanical action in the alimentary canal body does not assimilate it (Kaialy W *et al.*, 2014). (Yasir M

et al., 2010) has reported that Psyllium husk can be a promising polymer for gastroretentive floating drug delivery systems in combination with synthetic polymers. Kaialy W *et al also reported that* psyllium was proved to be a promising polymer to control the drug release in combination with other hydrocolloids.

(2) Carboxymethyl Cellulose (CMC)

Carboxymethyl cellulose (CMC) or cellulose gum is a cellulose derivative. It is commonly used in pharmaceutical industry as thickening agent and it is also used in ointments as a dispersant and humectant (11).

MATERIALS, EQUIPMENT AND METHODS

Materials: Metformin Hcl, b.no 150118 (Saif, Tunisia). Sodium salicylate(RIEDEL-DE HAEN AG SEELZE-HANNOVER, GERMANY). Psyllium husk powder (NOWFOOD,Glen Ellyn Rd). Sodium Carboxymethyl cellulose, high viscosity, BDH chemicals ltd, Poole England. Lactose, E.Merck, Darmstadt, Germany. Magnesium stearate, E.Merck, Darmstadt, Germany. Stearic acid , E.Merck, Darmstadt, Germany. Silicon dioxide, E.Merck, Darmstadt, Germany. Glucophage XR® 750mg, Merk Serono (SEMOY-FRANCE). Metforal® 850, laboratori GUIDOTTI S.P.A (Pisa-Italy).

Equipment: Balance- Sartorius BP 121S- Sartorius BL600, Canada. Granulator-Erweka AR 400, Germany. Oven-Memert UM 300, Germany. Tapping apparatus-Pharmatest PT-TD1, Germany, Fribilator- Pharmatest PTFE, Germany. Fourier transform infrared spectroscope (FTTIR)-IRPrestige, SHIMADZU, (Germany). Scanning electron microscope (SEM)- LEO, Germany, Dissolution apparatus- Pharmatest DT70, Germany. Uv/vis Spectrophotometer- JENWAY 6305, Germany.

METHODS

1-Preparation of the granules

1.1-Formulations (F1-F9) by wet granulation

Accurately Weighed quantity required (50g formula) of Metformin Hcl, Psyllium husk, Na Carboxy methyl cellulose and Lactose which is presieved 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 (mortar and pestle were used). The mixture was granulated using oscillating granulator. The granules were air dried at 55◦c for one hour then allowed to dry at room temperature. The granules were sieved through 1000µ sieve and the agglomerates were broken and lubricated with Mg stearate and silicon dioxide. The granules were stored in a desiccators for future use. The required dose was filled in hard gelatin capsules before the release studies (Niazi, 2009).

1.2-Formulations (F10, F11, SC1-SC5, SP1-SP5) by melting and congealing method

Accurately weighed quantity required from each ingredient in the formula, which is presieved through 450µ sieve. Stearic acid was melted at 75◦ c. 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 desiccator for future use. The required dose was filled in hard gelatin capsules before the release studies (Niazi, 2009).

System I: Psyllium husk and Carboxy methyl cellulose combinations as release retarding carriers.

Table I: Composition of formulations (F1-F6).

	F1	F2	F3	F4	F5	F6
API+Excipients	**Percent % (w/w)**	**Percent % (w/w)**	**Percent % (w/w)**	**Percent % (w/w)**	**Percent % (w/w)**	**Percent % (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 II: 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

A- stearic acid and Na CMC as release retarding carriers in different ratios.

Table III: Composition of formulations SC1-SC5.

	SC1	SC2	SC3	SC4	SC5
API+POLYMERS	**Percent % (W/W)**	**Percent % (W/W)**	**Percent % (W/W)**	**Percent % (W/W)**	**Percent % (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

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

Table IV: Composition of formulations SP1-SP5.

	SP1	SP2	SP3	SP4	SP5
API+POLYMERS	**Percent % (W/W)**	**Percent % (W/W)**	**Percent % (W/W)**	**Percent % (W/W)**	**Percent % (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

2- Physicochemical characterization of the granules

2.1-Angle of repose: Method: The fixed-funnel method was used to determine angle of repose. The granules were carefully poured through a funnel until the apex of the conical pile just touched the tip of the funnel. The height (h) of the pile of the Powder and the radius (r) of its conical base were measured and applied to compute the angle of repose (Θ) as in the following equation: $\Theta = \tan^{-1} h/r$, h=2cm

2.2-Bulk and tap densities

Method: 30 g of the granules sample were placed in a 100ml dry measuring cylinder and volume, $v_\circ$, weight of the granules without tapping, was determined. The cylinder was then given 500 taps using a tap density apparatus and the resulting volume, v500, was determined (12).

The bulk and tap densities were calculated using the following equations.

Bulk density (BD) = $w/v_\circ$ were w =30g

Tapped density (TD) = w/v500

- **Compressibility Index and Hausner Ratio**

The Compressibility Index and Hausner Ratio are measures of the propensity of a powder to be compressed. They are measures of the powder ability to settle and they permit an assessment of the relative importance of interparticulate interactions. In a free-flowing powder, such interactions are less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater interparticulate interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index and the Hausner Ratio (11).

Compressibility index (C %) = 100(TD-BD)/TD.

Hausner ratio: This parameter was calculated as the ratio of tap density to bulk density of the granules. Hausner ratio= TD/BD.

3-Fourier Transform Infrared Spectroscopy (FTIR)

FTIR is commonly used to identify compounds. It is used to identify drugs, Excipients and polymorphism, FTIR data has been utilized for the confirmation of cross linking in the polymeric network, the presence of interactions and identification of the changes in the functional groups (Setiawan, Rise, Moore, 1994).

4- In vitro release study

Drug release studies were conducted using the USP dissolution apparatus-1, basket-type, at a rotational speed of 100 rpm at 37±0.5°C. The dissolution media used were 900 mL of phosphate buffer solution (pH 6.8). Sink condition was maintained through out the whole experiment. Samples (5 mL) were withdrawn at predetermined time intervals and the same volume of fresh dissolution medium was replaced to maintain the volume constant. The withdrawn samples were filtered through a 0.45-μ membrane filter and the drug content in each sample was analyzed after suitable dilution with a UV spectrophotometer at 232 nm. The dissolution test was performed in triplicate, the content of drug was derived from a standard Metformine Hcl/S.S calibration curve then the drug dissolved at specified time periods was plotted as cumulative percent release versus time (h) curve (Siahi-Shadbad et al., 2011).

RESUTLS AND DESCUSION

I- Physicochemical characterization

Table V: Physicochemical properties of Metformin granules.

Formulation code	Bulk density (g/ml)	Tapped density (g/ml)	*Angle of repose (o)	Carr's index (%)	Hausner ratio
F1	0.42	0.48	28.4± 0.07	12.50	1.14
F2	0.45	0.50	27.1±0.93	9.62	1.11
F3	0.56	0.61	29.7±1.30	8.20	1.08
F4	0.47	0.52	28.4±0.89	10.00	1.10
F5	0.50	0.56	29.0±0.67	10.70	1.12
F6	0.56	0.61	29.7±0.69	8.20	1.09

* mean ±SD (n=3).

Table 6 shows the bulk density of the granules which are ranged from (0.31-0.56 g/ml) and tapped density from (0.33-0.61g/ml). The angle of repose was in the range (27.1-30.4°) and the compressibility (Carr's index) for all the formulations was < 25% while Hausner ratio was in the range (1.06-1.14).

Formulations F3 and F6 had the largest bulk and tapped densities which indicate that they had smallest granules where formulation F9 had the smallest bulk, tapped densities and largest granules this finding is probably due to the fact that the density of a material depends on the shape and size of the particles. The density is normally proportional to the number of spherical particles present in the bulk, and inversely proportional to the size of particles.

The granules in formulations F3 and F6 may be more regular in shape, producing a more uniform distribution, with smaller void spaces between the particles.

Carr's index of values < 25% indicates adequate granule flow and good flow properties.

The Hausner ratio is usually related to the compressibility of the powder and values < 1.25 are indicative of good compressibility (Nanjwade, Mhase, Manvi, 2011).

All formulations had Carr's index < 25% and Hausner ratio ≤ 1.14 indicating good to passable flow.

II- FTIR

The FTIR spectra for the tested formulations were compared with the spectrum of standard Metformin Hcl (figures 1-2). The percentages of the compatibility between the formulations spectra and the RS spectrum were in the range of (91.3-93.9%) which is acceptable according to the Japanese pharmacopeia specifications. These specifications state that when the percentage of compatibility between formulations spectra rises above 90%, these samples are considered to be identical. This finding proves that the drug was not affected by formulation process and the drug is fully compatible with the polymers used.

III- In vitro release studies

System I (F1-F6)

By reviewing table VI and figures (3), a consistent significant decrease in the percentage of drug released after 4hrs (90±1.10%-86±0.81%-81.9±2.0%-72±1.12%-68.4±2.20%) can be noticed as the concentration of Na CMC is increased in the formulations. In addition that, it is also worth mentioning that when the ratio of Psyllium Husk to Na CMC reaches (1:1), a considerable reduction in the percentage drug released was clear 82.8%. This finding is consistent with that reported in the literature where, (Siahi-Shadbad et al., 2011) found out that there was a synergistic effect in sustaining the drug release between Psyllium and Na CMC. In addition to that, (Chavanpatil et al, 2006) have shown that The swelling property of Psyllium was found to be greater than that of HPMC but it is taking a longer time to swell. This property is found to be in accordance with that reported by (Yasir *et al*., 2010), in which they found that the formulation containing Psyllium Husk took about 6 to 8 hours to complete swell as compared to the formulation prepared with HPMC that took 4-5 hours to complete swell. In the first hour of this study, the swelling index for formulation prepared with Psyllium alone was 57.1% and 85.92% for the formulation prepared with HPMC alone.

Table VI: percentage of Metformin released from formulations F1-F11 vs. time.

Time hrs	Cumulative % drug released	Cumulative % drug released	Cumulative % drug released	Cumulative % drug released	Cumulative % drug released	Cumulative % drug released	Cumulative % drug released	Cumulative % drug released
0.5	18.0	12.6	11.7	12.6	9.9	8.1	8.1	9.0
1	36.9	22.5	24.3	31.5	19.8	43.2	43.2	18.0
1.5	50.4	43.2	43.2	43.2	36.9	48.6	48.6	33.3
2	72.0	57.6	54.9	48.6	48.6	52.2	52.2	43.2
3	84.6	84.6	81.9	66.6	68.4	81.0	81.0	52.2
4	90.0	86.4	93.6	72.0	84.6	82.8	82.8	66.6
7	95.4	108.0	99.0	93.6	96.3	93.6	93.6	84.6

Formulations (F10, F11)

A hydrophobic polymer (Stearic acid) was used in formulations (F10,F11) in combination with a hydrophilic polymer Na CMC to improve the drug release characteristics as shown in table VI and figure (3) where two different concentrations of stearic acid were used (13%-71.4%) the percentage of drug released after 4 hrs was (63±0.93%-66.6±1.90%) respectively. At low concentration of stearic acid in the formulation (F11) a decrease in the percentage of the drug released is expected to be low due to the increased lipophilicity of the matrix (Hamdani, Moes, Amighi, 2002).

Furthermore, penetration of the dissolution fluid was hindered by the hydrophobic coating of stearic acid around the drug particles, leading to diminished drug release over extended period (Yonezava, Ishida, Sunanda, 2001).

The increase in the percentage of stearic in the formulations studied, has resulted in a proportional increase in the percentage of drug released over 7hours as shown in table 19 and figure 11. This finding is probably attributed to the fact that the solubility of stearic acid is about 1g/l at 37°c compared to 0.003g/l at 20° c (Higuchi, 1963). This increase in solubility of stearic acid at 37° c is expected to create cracks, pores and channels, which allows the drug to dissolve and leach out of Na CMC matrix at higher rate.

System II

The fact that a freely soluble drug with a large dose such as Metformin, is extremely difficult to formulate into a controlled release drug delivery system, has prompted us to look for a model drug with much smaller dose. Our choice was Sodium Salicylate which was tested in system II. By reviewing tables (VII, VIII) and figures (4, 5 - 6,7), it is possible to conclude that by decreasing the percentage of stearic acid and increasing the percentage of the hydrophilic polymers (Na CMC and Psyllium Husk) in these formulations has resulted in a significant drop in the amount of drug released after 7 hours. The cumulative percentage of drug released at 7 hrs were (SC1-SC5) (69.6±0.67%- 45.8±1.54%) and (SP1-SP5) (78.37±0.72%-53.08±0.21%) respectively. When comparing the effect of a hydrophilic polymer in both groups the amount of drug released from Na CMC formulations (SC) was less than that of Psyllium formulations (SP), as discussed earlier may be due to longer swelling time of Psyllium when compared with Na CMC (Yasir *et al*, 2010).

Table VII: percentage of sodium salicylate released from formulations (SC1-SC5).

Time hrs	*SC1 Cumulative % drug released	*SC2 Cumulative % drug released	*SC3 Cumulative % drug released	*SC4 Cumulative % drug released	*SC5 Cumulative % drug released
0	**0**	**0**	**0**	**0**	**0**
0.5	16.80± 1.10	18.00± 0.40	15.60± 1.16	12.00± 0.75	8.40± 1.06
1.0	23.00± 0.60	24.10± 0.81	24.09± 0.32	15.67± 1.32	9.65± 0.92
1.5	25.00± 0.45	25.30± 0.84	26.50± 0.07	20.49± 1.17	14.45± 1.09
2.0	30.00± 0.73	26.54± 1.31	36.15± 0.09	26.60± 0.45	21.68± 0.38
3.0	52.80± 1.07	49.35± 0.62	48.20± 0.48	34.90± 1.02	27.70± 0.97
4.0	55.20± 0.92	57.87± 0.35	51.87± 1.05	39.80± 1.53	32.60± 1.11
7.0	69.60± 0.67	69.90± 0.50	66.28± 1.10	57.80± 2.03	45.80± 1.54
	P ≤ 0.002	P ≤ 0.002	P ≤ 0.001	P ≤ 0.003	P ≤ 0.004

* mean ± S.D. (n=3)

Table VIII: percentage of sodium salicylate released from formulations (SP1-SP5).

Time hrs	SP1 Cumulative % drug released	SP2 Cumulative % drug released	SP3 Cumulative % drug released	SP4 Cumulative % drug released	SP5 Cumulative % drug released
0	0	0	0	0	0
0.5	10.80± 0.05	7.20± 0.04	7.20± 0.05	4.80± 0.22	4.80± 0.07
1.0	22.86± 0.93	14.44± 0.31	15.64± 0.05	18.03± 0.35	14.43± 0.84
1.5	37.33± 0.81	26.48± 0.57	21.69± 0.22	24.10± 0.42	21.68± 0.35
2.0	55.40± 1.07	32.55± 0.83	31.32± 0.17	31.30± 0.40	31.30± 0.79
3.0	61.50± 1.27	43.38± 0.90	43.37± 0.63	39.70± 0.10	39.70± 0.65
4.0	66.34± 0.55	55.44± 0.35	53.04± 0.45	51.80± 0.45	50.60± 0.30
7.0	78.37± 0.72	72.32± 1.16	60.29± 1.11	54.29± 0.13	53.08± 0.21
	p≤ 0.002	p≤ 0.006	p≤ 0.004	p≤ 0.003	p≤ 0.004

* mean ± S.D. (n=3)

LIST OF FIGURES

1- FTIR spectrum for standard Metformin.
2- FTIR spectrum for formulation F3 (91.3% Related to RS).
3- Percentage of Metformin released from formulations F1-F11 vs. time.
4- Percentage of sodium salicylate released from formulations (SC1-SC5) vs. time.
5- Percentage of sodium salicylate released from formulations (SP1-SP5) vs. time.
6- Cumulative percentage of drug released at 7 hrs of dissolution time in different stearic acid and Na CMC concentrations, formulations (SC1-SC5).
7- Cumulative percentage of drug released at 7 hrs of dissolution time in different stearic acid and Psyllium husk concentrations, formulations (SP1-SP5).

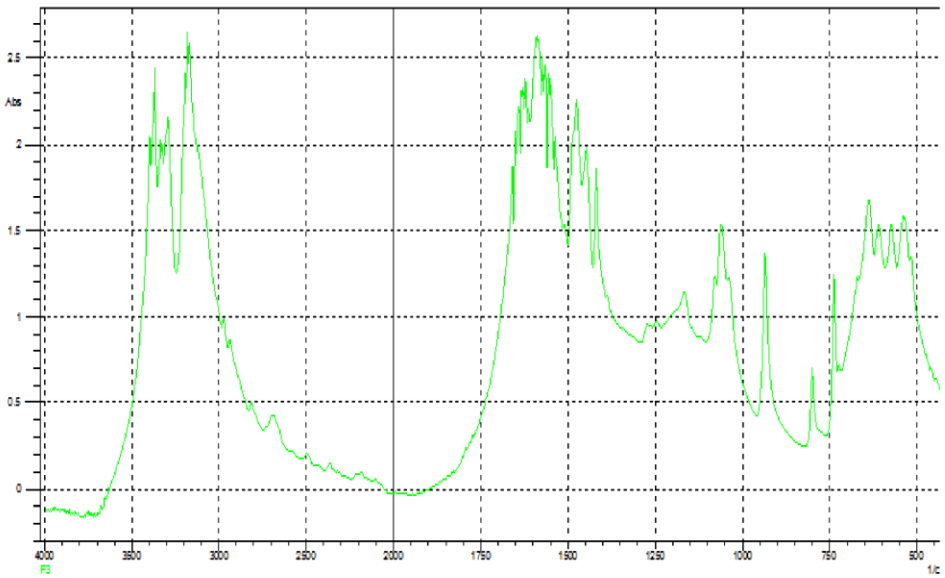
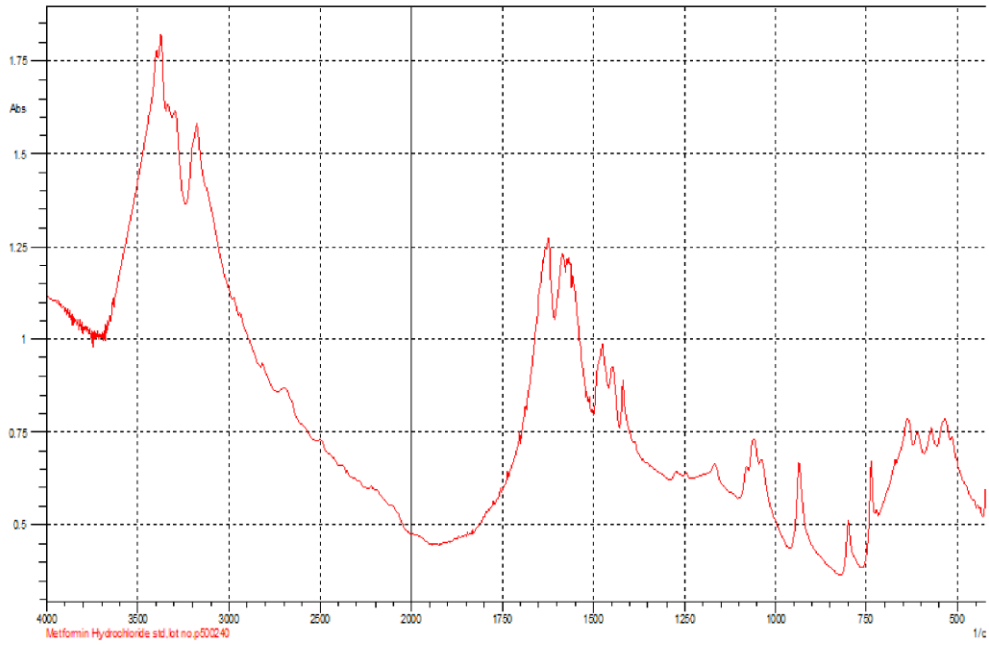


Figure 1.



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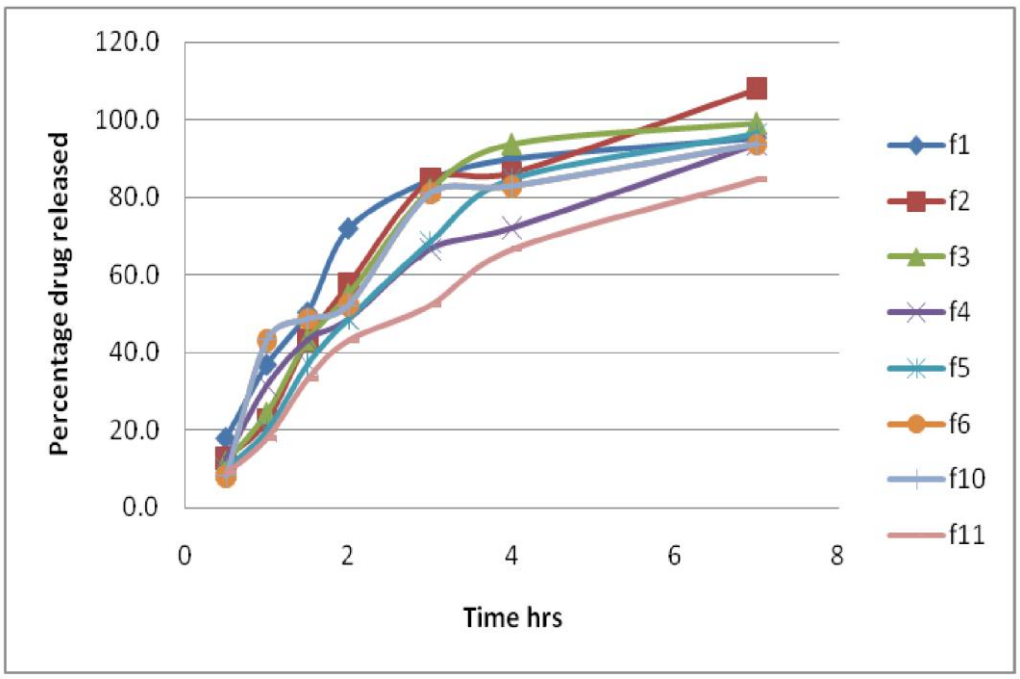

Figure 3.

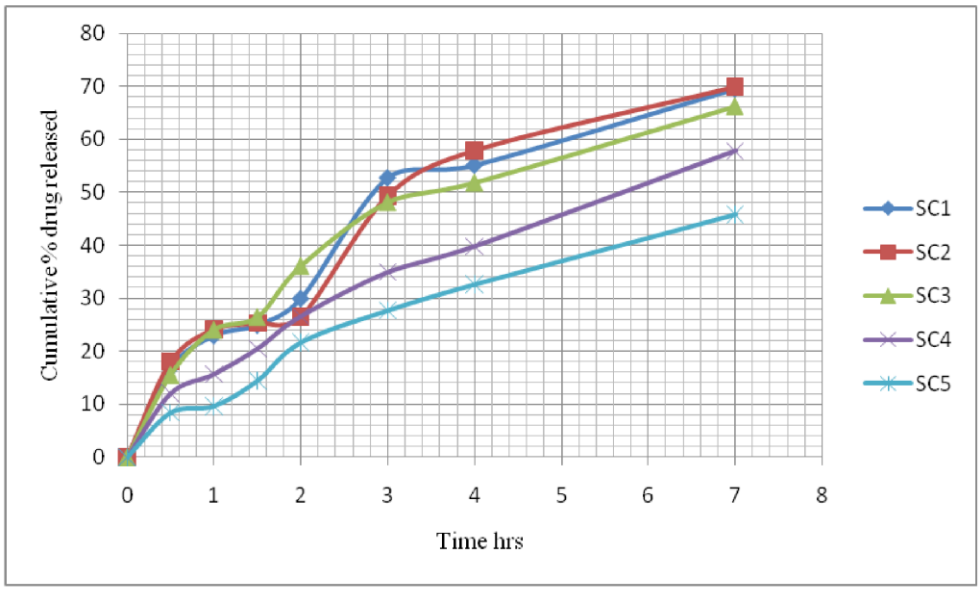

Figure 4.

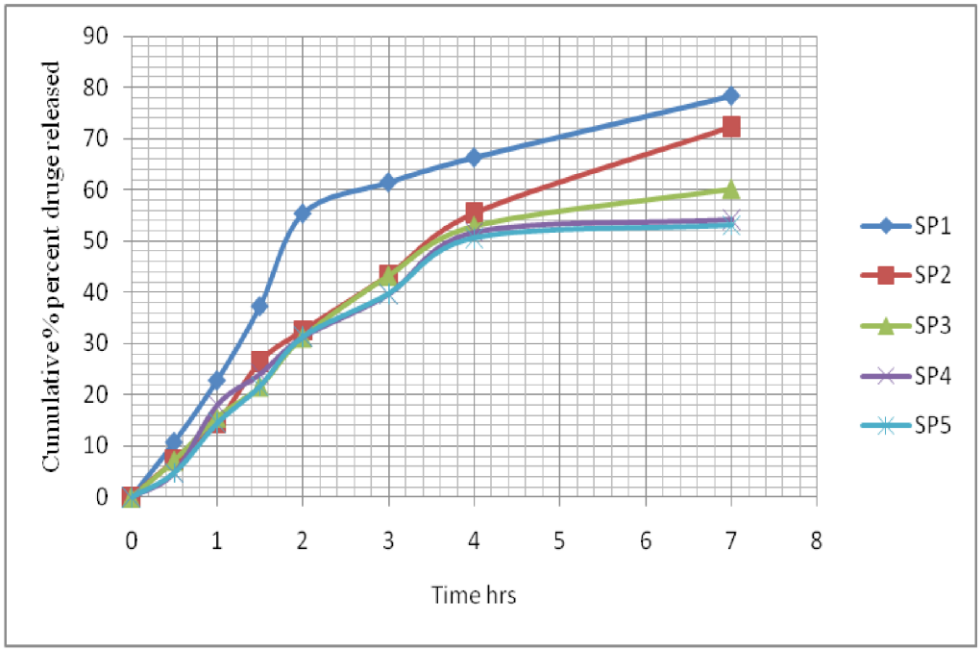

Figure 5.

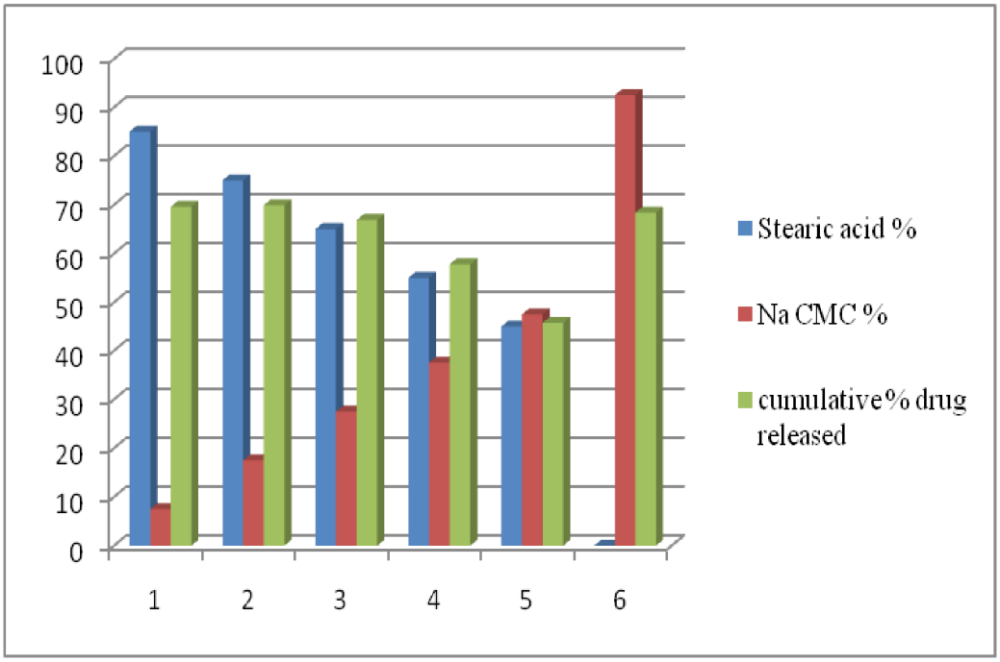

Figure 6.

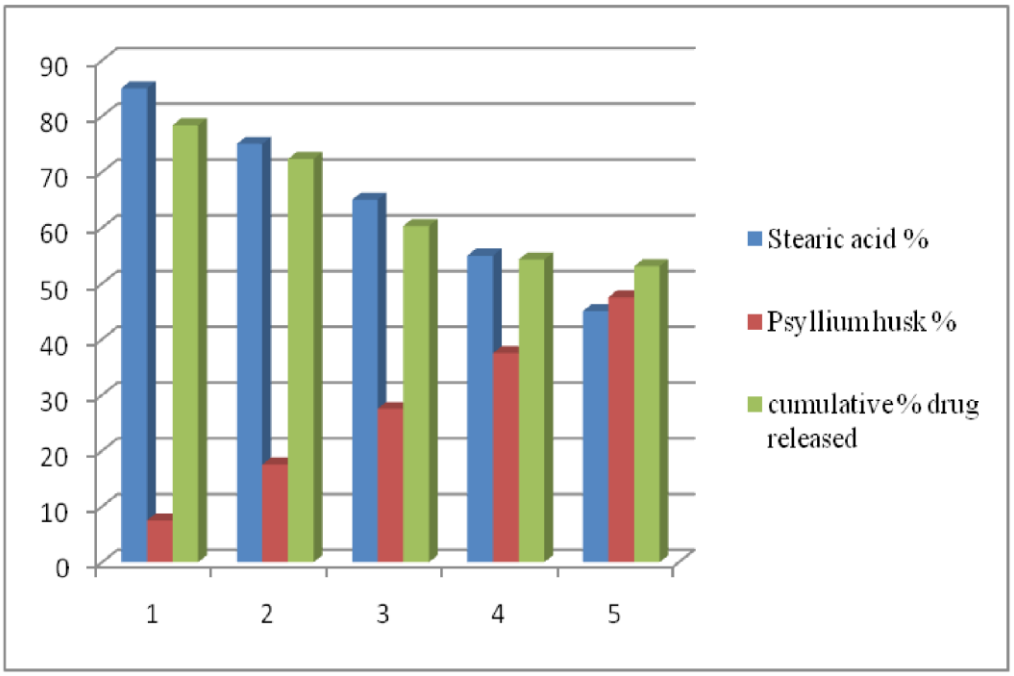

Figure 7.

REFERENCES

1. Chavanpatil M, Jain P, Chaudhari S, Shear R, Vavia P. Novel sustained release, swellable and bioadhesive gastroretentive drug delivery system for ofloxacin. *Int .J .Pharm*, 2006; 316(1-2): 86-92.
2. Hamdani J, moes A, amighi K. Development and evaluation of prolonged release pellets obtained by the melt pelletization process. *Int. J. Pharm*, 2002; 245: 167-177.
3. Higuchi T. Mechanism of sustained-action medication: Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. *J. Pharm Sci*, 1963; 52: 1145-1149.
4. Kaialy W, Emami P, Asare-Addo K , S. Shojaee S, Nokhodchi A. Psyllium: a promising polymer for sustained release formulations in combination with HPMC polymers. *Pharm Dev Technol*, 2014; 19(3): 269-77.
5. Nanjwade B, Mhase S, Manvi F. Formulation of extended release Metformin hydrochloride matrix tables. *Tropical journal of pharmaceutical research*, 2011; 10(4): 375-383.
6. Niazi S. Hand book of pharmaceutical manufacturing formulations, CRC press, 2009.
7. Setiawan Y, Rise T, Moore D. Fourier transform infrared (FTIR) spectrometry for the assay of polyhedral Boron compounds in plasma and pharmaceutical formulations, *Pharmaceutical research*, 1994; 11(5): 8.
8. Siahi-Shadbad M, Asare-Addo K, Azizian K, Hassanzadeh D, Nokhodchi A. Release Behaviour of Propranolol HCl from Hydrophilic Matrix Tablets Containing Psyllium Powder in Combination with Hydrophilic Polymers, *AAPS. Pharm. Sci. Tech*, 2011; 12(4): 1176–1182.
9. Yasir M, Asif M, Bhattacharya A., Bajpai M. Development and evaluation of gastroretentive drug delivery system for the theophllyne using Psyllium husk. *Int J Chem tech research*, 2010; 2: 792-799.
10. Yonezava Y, Ishida S, Sunanda S. Release from or through a wax matrix system:I basic release properties of the wax matrix. *Chem Pharm Bull*, 2001; 49: 1448-1451.
11. http://www.sino-cmc.com/html_products/Sodium-Carboxymethyl-Cellulose-Pharmaceutical-Grade-28.html.
12. https://learn.pharmacy.unc.edu/pharmacopedia/pharmaceutics411/index.php/Oral_Modified_Release_Dosage_Forms.
13. https://en.wikipedia.org/wiki/Stearic_acid