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Formulation and Evaluation of Gastroretentive Floating Microballoons of Anti diabetic drug

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ABSTRACT

The objective of present investigation is to design a sustained release floating microballoons of Metformin HCl using two polymers of different permeability characteristics Cellulose Acetate Butyrate (MW of 16,000) and Eudragit RS 100 (MW of 150,000) using the oil-in-oil emulsion solvent evaporation method. The prepared microballoons were studied for drug release behavior in simulated gastric fluid at pH 1.2 and phosphate buffer at pH 6.8 respectively. Polymers were used separately and in combination (1:1) to prepare different microballoons using acetone as organic phase. In all batches of microballoons, the total polymer concentration was kept constant (10%w/w). No significant differences in drug loading for microballoons made of different polymer to polymer ratios were noted. Drug loaded microballoons were found to float on 0.1M HCl for more than 8 hour. FT-IR study showed no drug polymer interaction as evident from the FT-IR spectra. SEM study clearly reveals the smoothness of the spherically shaped particles. All the prepared microballoons showed higher amount of drug release in phosphate buffer (pH 6.8) as compared to the release in 0.1M HCl (pH 1.2). Evaluation of the release data reveals that microballoons prepared from RS 100, CAB and combination of both the polymers exhibit Higuchi spherical matrix release, followed by first order and zero-order release kinetics.

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INTRODUCTION

Despite tremendous advancement in the drug delivery system, oral route remains the preferred route for the administration of therapeutic agents and because of low cost therapy and ease of administration leads to higher levels of patient compliance. Conventional oral dosage forms such as tablets, capsules, provide specific drug concentration in systemic circulation without offering any control over drug delivery and also cause great fluctuations in plasma drug levels. The design of oral controlled drug delivery system should be primarily aimed to achieve more predictable and increased bioavailability. An incomplete release of the drug and shorter residence time of the dosage forms in the upper GIT, which is a prominent site for the absorption of many drugs, leads to decreased bioavailability. Metformin HCl, which is an antihyperglycaemic agent widely used in the management of NIDDM.

Stepensky et al[1] concluded that absolute oral bioavailability of Metformin HCl is 50-60% due to its site-specific absorption limitations. It is safe drug and it has a half-life of 1.5-3 hrs. It is not absorbed completely and gives low bioavailability problem[2]. Almost 80-100% of the drug is excreted unchanged[3]. The total daily requirement of Metformin HCl is 1.5-3g/day. Henceforth, there being high incidence of GI side effects and toxicity. Therefore, there are continued efforts to improve the pharmaceutical formulation of metformin hydrochloride in order to achieve an optimal therapy. These efforts mainly focus on controlled/slow release of the drug including the sophisticated gastro- retentive systems. However, bioavailability of the drug has been found to be reduced further with controlled release dosage forms, probably due to the fact that passage of the controlled release single unit dosage forms from absorption region of the drug is faster than its release and most of the drug released at the colon where metformin hydrochloride is poorly absorbed[3, 4].

Controlled release formulation suitable for metformin hydrochloride, therefore, should be a gastro-retentive dosage form[1], which releases the drug slowly in the stomach for gradual absorption in the intestines. The slow but complete drug release in the stomach is expected to increase bioavailability of the drug as well its complete utilization which may results to, lower dose and GI side effects. Multi unit dosage forms are considered to release the drug at a controlled rate and remain in the stomach for a prolonged period with much less chance of dose dumping. Furthermore they are supposed to cause less gastric adverse reactions and are insensitive to concomitant food intake, thereby reducing inter and intra-patient variability and increasing the predictability of the dosage form.

The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion, flotation, sedimentation, expansion, modified shape systems, or by the simultaneous administration of pharmacological agents that delay gastric emptying[4-5]. Among the different approaches that have been developed, low density system holds promise. Floating DDS systems are low density systems that have sufficient buoyancy to float over gastric contents, and the drug is released slowly at the desired rate, which results in increased gastro-retention and reduces fluctuations in plasma drug concentration. Both natural such as chitosan[6] and synthetic polymers (polycarbonate[7], polyacrylate[19], polymethacrylate,[12,13] polystyrene[9], ethyl cellulose[16], cellulose acetate[12,13]etc.) and some novel excipients like calcium silicate[10], low density foam powder 8 have been used to achieve floatation. One of the methods to prepare such floating microballoons is the emulsion solvent evaporation method[6-7]. However literature survey revealed that very few works have been carried out so

far to prepare floating microballoons of metformin HCl.

Rao et al[16] designed floating microballoons of metformin HCl using hydrophilic polymers, and concluded that HPMC has better floating ability than other hydrophilic polymers, but it cannot control the drug release for extended period of time. Ray et al[17] prepared floating controlled microballoons of metformin HCl by emulsion solvent evaporation method using ethyl cellulose as retardant polymer. He, however reported that the prepared microballoons have minimum floating tendency, but exhibited satisfactory drug release kinetics close to the marketed extended release tablet formulations. Therefore, it seemed reasonable to develop a gastro-retentive DDS of metformin HCl with improved buoyancy in order to optimize the pharmacokinetics and pharmacodynamics of the drug. So, the objective of present investigation is to design a sustained release floating microballoons of Metformin HCl using two polymers of different permeability characteristics Cellulose Acetate Butyrate (MW of 16,000) and Eudragit RS 100 (MW of 150,000), in order to achieve an extended retention in the upper GIT, which may result in enhanced absorption and thereby improved bioavailability. The microballoons were evaluated for size, buoyancy and incorporation efficiency. The prepared microballoons were also studied for drug release behavior in simulated gastric fluid at pH 1.2 and phosphate buffer at pH 6.8 respectively, and optimize the drug release to match the target release profile and possible release mechanism proposed.

MATERIALS AND METHODS
Materials:
Metformin HCl was obtained as a gift sample from Alembic Pvt. Ltd. Baroda, Gujarat. Cellulose Acetate Butyrate (Mol. Wt 16,000) was obtained as a gift sample from Cipla R&D Centre, Vikhroli, Mumbai,

(Manufacturer- Eastman Chem. Co, U.S.A.) and Eudragit RS 100 (Mol. Wt 150,000) was obtained from Rohm Pharma, GmbH, Darmstadt, Germany. Acetone, liquid Paraffin (Light), Span 80 AR, Magnesium stearate was purchased from Ranbaxy fine Chemicals Ltd. Mumbai, India. All other chemicals used were of analytical grade.

Method
Preparation of floating microballoons:
Microballoons containing highly water-soluble drug metformin HCl were prepared by nonaqueous emulsion solvent evaporation method.[11-13] Eudragit RS 100 (10% w/w) and Cellulose acetate butyrate (10% w/w) were used separately, and mixed together to form microballoons. In case of microballoons made of combination polymers, firstly weighed quantity of eudragit RS 100 and CAB was completely dissolved in acetone at the polymer ratio 1:1, but the total concentration of the polymer was kept constant (10% w/w in acetone). 5% w/w of magnesium stearate (to the total polymer conc. used) and weighed quantity of Metformin HCl (50%w/w) were dispersed to the above slurry and stirred in a magnetic stirrer. The drug polymer dispersions were pressurized under CO_2 gas, which upon release of the pressure form cavities on the polymeric surface[13]. The porous drug polymer dispersions were then slowly introduced into 70 ml liquid paraffin previously emulsified with 1 % Span 80, while stirring at 1000 rpm held by a mechanical stirrer (Remi, Mumbai) equipped with a three-blade propeller at room temperature. The whole system was stirred for 3 hour to allow the complete evaporation of acetone. The oil layer was decanted and microballoons were washed several times with petroleum ether (40-60º). The washed microballoons were dried in an oven at room temperature not exceeding 25ºC. The detail composition of each formulation was given in Table 1.

Viscosity of the Polymer Organic Phase:

Relative viscosities of the polymer solutions were determined with an Ostwald viscometer; since the solutions have relatively low viscosities and the polymer solutions can be considered to have Newtonian type of flow[12].

Yield of Microballoons:

The prepared microballoons with a size range of 371-381μm were collected and weighed. The measured weight was divided by the total amount of all nonvolatile components which were used for the preparation of the microballoons.

% Yield = (Actual weight of product / Total weight of excipient and drug) × 100

Particle size analysis:

Size distribution was determined by sieving the microballoons using a nest of standard BSS sieves (36, 44, 25) as well as by optical microscopy.

Scanning electron microscopy:

For morphology and surface characteristics14, prepared microballoons were coated with gold in an argon atmosphere. The surface morphology of the microballoons was then studied by Scanning Electron Microscope (Hitachi S-3600N Scanning Electron Microscope, Japan).

Fourier Transform Infrared Spectroscopy (FT-IR):

Drug-polymer interactions were studied by FT-IR spectroscopy14. The spectra were recorded for pure drug and drug-loaded microballoonsusing FT-IR (PerkinElmer, Model No. 883). Samples were prepared in KBr disks (2 mg sample in 200 mg KBr). The scanning range was 400-4000 cm^{-1} and the resolution was 2 cm^{-1}.

Drug entrapment efficiency:

Microballoons equivalent to 100 mg of pure drug were crushed and added to 50 ml of 0.1M HCl, pH 1.2. The resulting mixture was shaken in a mechanical shaker for 3 h to completely extract the drug. The solution was filtered with a Whatman filter paper and 1 ml of this solution was appropriately diluted to 25 ml using 0.1M HCl, pH 1.2, and analyzed spectrophotometrically at 233 nm using UV-Visible double beam Spectrophotometer (1700, Shimadzu, Japan)[18].

$$D.D.E\ \% = \frac{\text{Amount of drug actually present}}{\text{Theoretical drug load expected}} \times 100$$

In vitro Evaluation of Floating Ability:

An in vitro floating study was carried out in simulated gastric fluid using USP type II dissolution apparatus containing 0.02% Tween 80 as a dispersing medium[19-20]. Microballoons were spread over the surface of 500 ml of dispersing medium at 37 ± 0.5ºC. A paddle rotating at 100 rpm agitated the medium. Each fraction of microballoonsfloating on the surface and those settled down were collected at a predetermined time point (upto10 hr). The collected samples were weighed after drying.

$$\% \text{ floatability} = \frac{\text{Wt. of floating microspheres after drying}}{\text{Wt. of floating + settled microspheres after drying}} \times 100\ \%$$

In vitro Drug Release Study:

In vitro drug release studies[20-23] was carried out for all products in USP type II fitted with six rotating basket [Campbell Electronics, Mumbai, India] dissolution test apparatus). The microballoons were evaluated for drug release using 900 ml of simulated gastric fluid (pH 1.2) and simulated intestinal fluid (pH 6.8) for 10 hour maintained at 37 ± 0.1°C and stirred at 100 rpm. 2 ml of aliquots were withdrawn at different time intervals and an equivalent volume of medium prewarmed at 37°C was added to maintain sink condition.

Withdrawn samples were analyzed spectrophotometrically at 233 nm using a UV-Visible double beam Spectrophotometer (1700, Shimadzu, Japan). The dissolution profiles of the prepared formulations were compared with that of the marketed formulations to arrive at the target release. The selected formulations were tested for a period of 8 weeks at different storage condition of 25^0C and 40^0C with 60% RH and 75% RH, to evaluate their drug content.

Kinetic Assessment:

Drug release from the prepared microballoons made of eudragit RS 100, CAB and mixture of two polymers were kinetically evaluated to fit to zero order, first order, Higuchi kinetic and Korsemeyer-peppas models.[24-26]

RESULTS AND DISCUSSION:

Microballoons containing highly water-soluble drug metformin HCl were successfully encapsulated into microballoons using two polymers of different permeability characteristics. The present study was aimed at not only to improve the buoyancy of microballoons, but also to release the drug in the acidic pH in controlled fashion. Also, to make a formulation having density lower than the gastric contents, using mixture of two polymers of different permeability characteristics. The polymers used in the fabrication of microballoons were well established polymers for the said dosage form. The two polymers are selected in such a way that one will give initial burst release, which is essential from therapeutic point of view, while the other will control the drug release by maintaining the buoyancy. Eudragit RS 100 contain higher amount of quaternary ammonium groups, which renders it more permeable. It was evident that addition of eudragit RS 100 increased the permeability of the microballoons to the surrounding dissolution medium due to the swelling nature of the polymer (Bodmeier and Chen et al[14]).

In addition to this, the porous nature of the microballoons produces an upward motion of the dosage form to float on the gastric contents. Hence, the fabricated low density system has been found to be promising over, conventional tablet formulations, as it releases the drug slowly in the stomach for gradual absorption in the intestines. The slow but complete drug release in the stomach is expected to increase bioavailability of the drug as well its complete utilization which may results to, lower dose and GI side effects. The compositions and physical characterization of the drug made of eudragit RS 100 and cellulose acetate butyrate (CAB) were shown in Table 1. Standard conditions in all batches of microballoons formulations were surfactant concentration-1 % Span 80, quantity of Magnesium Stearate-5% w/w, volume of processing medium-70ml liquid paraffin, stirring speed-1000 rpm, conc. of total polymer solution 10% w/w in acetone. The prepared microballoons were porous, spherical and exhibited a good flow property.

In order to measure the relative viscosity of polymer solutions, different polymer concentrations were prepared in acetone and measured the viscosity using Ostwald viscometer. It is observed that CAB solutions have higher relative viscosities than those of eudragit RS 100, although the later has higher molecular weight. In addition to this, solutions prepared from different concentrations of two polymers at constant 1:1 ratio have resulted in higher relative viscosities than the single polymer solution viscosities. This synergistic increase in the relative viscosity could be due to an interaction between the two polymers of different molecular weight (Figure 1). The particle size of the microballoons prepared using 10% w/w eudragit RS 100, 10% w/w CAB and combination of both the

polymers at 1:1 ratio (total 10% w/w) differs significantly at the same stirring speed.

When the polymer to polymer ratio was 1:1, there was formation of microballoons with large and irregular sizes due to increase in solution viscosity of the polymers. Hence, higher agitation speed is required to prepare microballoons of same sizes as that of single polymers alone (Table 2). No significant differences in drug loading for microballoons made of different polymer solution viscosities were noted. However, the drug loading increases as the concentration of polymer is increased relative to drug concentration. The analysis of drug content showed maximum entrapment efficiency (85-90%) at the drug polymer ratio 1:2 (Table 2).

SEM study shows that particles made of eudragit RS 100 and CAB were spherical. The surface of the drug-loaded microballoons manifested the presence of drug particles, clearly visible from outside. Irregular surfaces and larger sizes were observed in the microballoons prepared from polymer to polymer ratio 1:1at the same stirring speed. Large aggregates of magnesium stearate were visible over the microballoons surface (Figure 3). Presence of pores were detected on the microballoons surface which increased in size and number after dissolution indicating leaching of the drug through these channels (Figure 4). FTIR spectra revealed that there was no such interaction between the drug and the polymers used for microballoons formulation.

The principle absorption peaks of metformin HCl appears at 3171 cm^{-1} due to the N-H stretching of the primary amine group (-NH2) and at 1062 cm-1 due to C-N stretching. However, a sharp peak at 1580 cm^{1} occurs due to N-H bending vibrations of the primary amine group. The identical peaks of N-H stretching, C-N stretching, N-H bending vibrations were also appeared in the spectra of Metformin loaded microballoons prepared with eudragit RS 100, CAB and combination of both the polymers (Figure 5).

In vitro dissolution studies:

In vitro dissolution studies of all batches of microballoons were shown in Table 3. Microballoons made of eudragit RS 100 showed good flow properties, maximum floating tendency, but faster in vitro drug release rate in both simulated gastric media (pH 1.2) and phosphate buffer (pH 6.8). The prepared microballoons made of eudragit RS 100 showed maximum drug release of 81-83% within 8-10 hours in 0.1M HCl (Figure 6). However, the same microballoons showed higher amount of drug release, 85-89% in phosphate buffer (pH 6.8) as compared to the release in 0.1M HCl (Figure 7).

Likewise, microballoons made of CAB showed good flow properties, minimum floating behaviour but slower rate of invitro drug release initiated by lag time in both the dissolution media, as compared to the eudragit RS 100 microballoons. It is observed from the release profile that around 59-67% drug released in 0.1M HCl and 67-71% drug released in phosphate buffer (pH 6.8) within 8-10 hours. These observations could be attributed to the fact that CAB microballoons have thick polymeric surface as compared to RS 100 microballoons. The thick polymeric barrier slows the entry of surrounding dissolution medium in to the microballoons and hence less quantity of drug leaches out from the polymer matrices of the microballoons exhibiting extended release.

The combination of both the polymers CAB and eudragit RS 100 at polymer-to-polymer ratio 1:1 resulted in different in vitro release profiles close to the release profile of CAB microballoons alone. These microballoons also have the additional advantage of improved floating ability as compared to the

microballoons prepared using CAB alone. It was also evident that combination of eudragit RS 100 and CAB imparts a synergistic increase in the relative viscosity compared to the single polymers. The addition of eudragit RS 100 to CAB polymer increases the permeability of the microballoons to dissolution medium due to the swelling nature of eudragit RS 100. Moreover, eudragit RS 100 contain higher amount of quaternary ammonium groups, which renders it more permeable. This would increase the porosity of CAB membrane and minimizes the lag time initiated by CAB microballoons. Moreover, the porous nature of the
microballoons increases the number of pores on the polymer surface, through which water can penetrate into dosage form and leaching out the drug. It is observed from the release profile that 73-77% and 77-81% drug released within 8-10 hours in 0.1 HCl and phosphate buffer respectively (Figure 6-7).

The combination polymer at polymer to polymer ratio 1:1 helps to leach out the drug from its matrices and exhibits an initial rapid drug release for the first 2 to 3 hours and then slower drug release which can be best explained by Higuchi's spherical matrix release (Table

4). The marketed XR tablet exhibit extended release up to 10 hour, and maximum of 83-91% drug released in 0.1M HCl within 8-10 hours (pH 1.2). The marketed product also showed slightly higher amount of drug release rates in phosphate buffer (pH 6.8) as compared to 0.1M HCl. (Figure 4-5).

In order to describe the kinetics of the release process of drugs from microballoons preparation, the data were fitted with different kinetics models. From the kinetic table it can be observed that the release of Metformin HCl from the eudragit RS 100 microballoons exhibit diffusional characteristics and highly correlated with Higuchi spherical matrix release, followed by first order and zero order (Table 4).

Stability Studies:
The percentage drug content at different temperatures after every two weeks is given in Table 5. Dissolution study of selected formulation A1B1 was carried out after subjecting the formulation for stability study. From the stability data, the formulation is found to be stable, because there was no significant change in the percentage amount of drug content.

Table 1: Composition of the prepared microballoons

Formulation Code	Drug/Polymer ratio	Polymer concentration 10% w/w	Quantity of magnesium Stearate % w/w	Stirring Speed (rpm)
A1	1:2	RS 100	5	1000
B1[a]	1:2	CAB	5	1000
A1B1[a]	1:2	RS 100, CAB (1:1)	5	1500
B1	1:2	CAB	5	1500
A1B1	1:2	RS 100, CAB (1:1)	5	1800

Table 2: Various formulation parameters for microballoons

Formulation Code	% Yield	Particle size in micron	Drug Entrapment Efficiency (%)	Buoyancy (%)
A1	75.3	371±3.7	89.35± 1.42	71.0±1.7
B1[a]	89.41	534±1.7	91.51± 1.12	65.7±3.6
A1B1[a]	91.13	710±1.4	90.15± 1.8	73.5±2.3
B1	71.4	376±1.2	87.31± 1.3	68.3±3.8
A1B1	85.21	381±0.98	92.07± 1.2	76.6±1.3

* All values are expressed as mean ± SD, n=3

Table 3: In vitro drug release profile data

| Time (hr)	Cumulative % drug released of coded formulations							
	in 0.1 M HCl at pH 1.2				in Phosphate buffer at pH 6.8			
	A1	B1	A1B1	MKT	A1	B1	A1B1	MK
1	43.59 ± 1.03	24.11 ±1.98	37.31 ±2.23	21.3 ±1.17	46.51 ±1.05	25.16 ±1.12	38.1 ±1.01	23.17 ±1.15
2	47.08 ±1.02	27.21 ±1.15	41.03 ±2.15	33.15 ±2.18	49.25 ±1.63	29.07 ±1.18	42.3 ±1.49	37.11 ±1.43
3	56.11 ±1.15	31.03 ±1.93	49.25 ±2.13	39.59 ±2.57	57.69 ±1.46	33.51 ±2.13	47.41 ±1.63	41.39 ±1.23
4	69.15 ±1.23	39.17 ±1.23	58.31 ± 2.35	48.91 ±1.8	71.85 ±1.23	41.25 ±2.23	61.05 ±1.87	53.22 ±1.47
5	74.21 ±1.93	47.51 ±1.03	64.17 ±1.97	57.07 ±2.23	73.49 ±1.89	49.69 ±2.43	66.31 ±1.98	59.71 ±1.56
6	77.16 ±1.54	53.79 ±1.12	67.52 ±2.96	68.33 ±1.54	79.71 ±1.57	56.22 ±2.47	69.43 ±2.13	67.33 ±1.41
7	79.51 ±1.29	57.88 ±1.99	71.69 ± 2.57	79.24 ±1.47	84.22 ±1.63	59.31 ±2.51	73.34 ±2.23	76.15 ±1.14
8	81.75 ±1.27	59.18 ±1.05	73.41 ±1.97	83.03 ±1.97	86.39 ±1.17	67.75 ±2.41	77.15 ±2.54	87.21 ±1.23
9	82.07 ±1.23	64.61 ±1.97	75.16 ±2.13	87.41 ±2.13	87.15 ±1.87	69.19 ±2.17	79.03 ±1.67	89.08 ±1.18
10	83.13 ±1.98	67.22 ±1.07	77.21 ±1.98	91.57 ±2.57	89.61 ±1.56	71.81 ±1.98	81.35±1.17	94.55 ±1.12

#All values are expressed as mean ± SD, n=3

Table 4: Kinetic evaluation of drug release data for microballoons formulations

Formulation Code	Kinetic Models							
	Zero Order		1st Order		Higuchi Model		Korsemeyer Pappas Model	
	R^2	k_0	R^2	k_1	R^2	k_H	R^2	n
A1	0.7531	6.62	0.9362	0.063	0.9334	20.49	0.8411	0.032
B1	0.9302	6.02	0.9877	0.043	0.9721	22.10	0.9392	0.052
A1B1	0.8095	6.26	0.9794	0.051	0.9741	20.21	0.8931	0.034
MKT	0.9671	8.82	0.9669	0.108	0.9771	7.51	0.8716	0.066

Table 5: Result of stability studies

Time		% Drug content of formulation A1		% Drug content of formulation B1		% Drug content of formulation A1B1	
		At 25^0C	At 40^0C	At 25^0C	At 40^0C	At 25^0C	At 40^0C
After weeks	2	98.5	96.16	98.7	97.2	98.61	97.17
After weeks	4	98.10	95.08	97.5	96.8	97.49	96.8
After weeks	6	98.31	94.50	96.8	96.13	96.6	95.5
After weeks	8	97.54	93.13	96.3	95.6	95.8	95.12
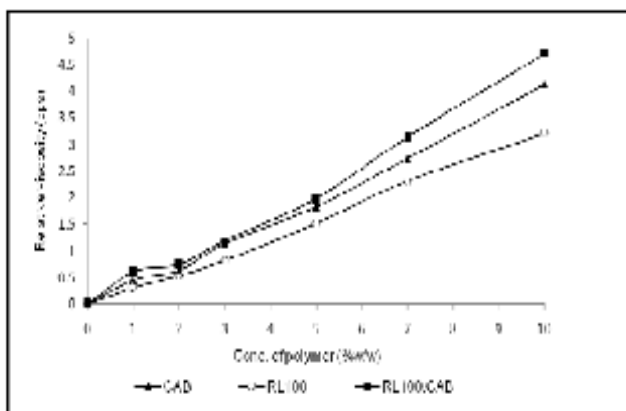
Fig.1: Relative viscosities of different concentration of eudragit RS 100, CAB and combination of both the polymers at 1:1 ratio.
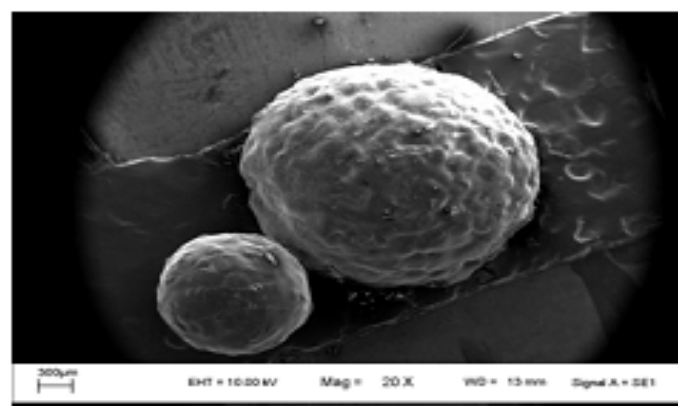
Fig. 2: SEM photographs of drug loaded microballoons made of eudragit RS 100 and cellulose acetate butyrate polymers before dissolution
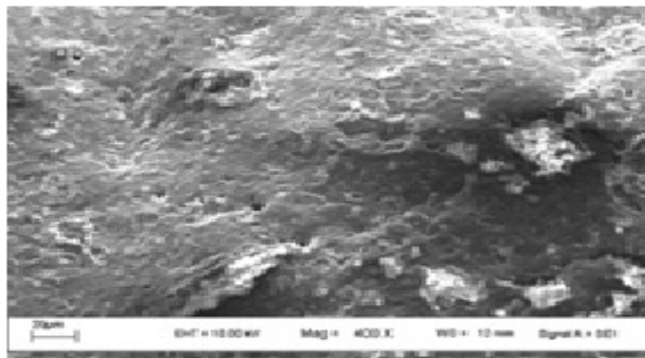
Fig. 3: SEM photographs of drug loaded microballoons made of eudragit RS 100 and cellulose acetate butyrate polymers after dissolution
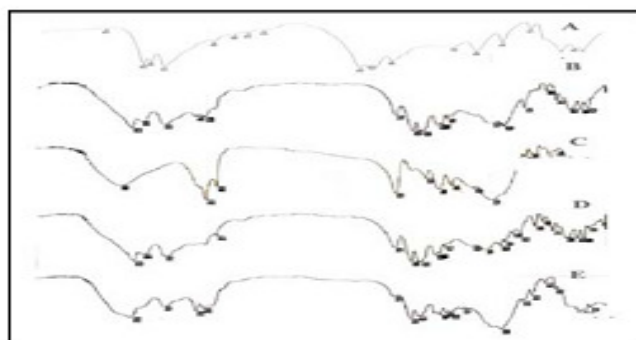

Fig. 4: Comparative study of the FT-IR spectrum of pure drug (A), drug loaded RS 100 and CAB (B),blank RS 100 and CAB (C), drug loaded RS 100 (D) drug loaded CAB   (E) microballoons
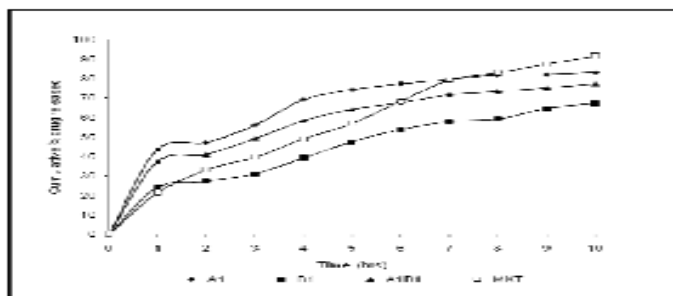

Fig. 5: Comparison of in vitro drug release profiles of drug loaded microballoons with marketed product in 0.1M HCl (pH 1.2). A1-RS 100 microballoons, B1-CAB microballoons, A1B1-RS 100, CAB microballoons, MKTmarketed extended release tablet.
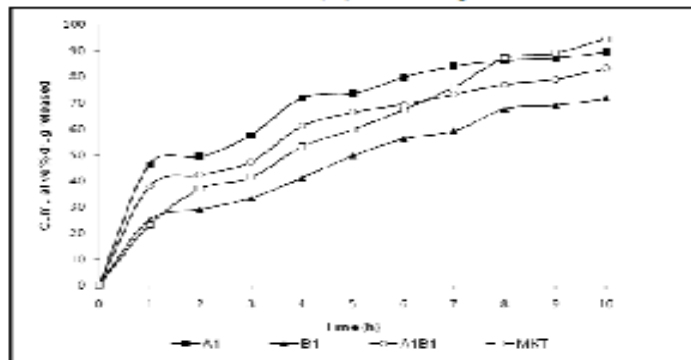

Fig. 6: Comparison of in vitro drug release profiles ofdrug loaded microballoons with marketed product in phosphate buffer (pH 6.8). A1-RS 100 microballoons, B1-CAB microballoons, A1B1-RS 100, CAB microballoons, MKT-marketed extended release tablet.

CONCLUSION

The present investigation of gastric floating microballoons of Metformin HCl was successfully prepared by using two polymers of different permeability characteristics. CAB has high butyryl content and it is insoluble at physiological pH values. CAB microballoons extend the drug release for longer period of time, with an initial slow release at the first one-hour and then controlled release for the rest period of time. But, microballoons made of both the polymers at 1:1 ratios (total 10% w/w) exhibited satisfactory drug release pattern, as it released the drug in controlled fashion for extended period of time by maintaining the buoyancy. Although, metformin extended release tablet formulations were well established, but it causes a great fluctuations in plasma drug levels and fail to improve the bioavailability.

But microballoons formulation offer several advantages over other sustained release systems, especially matrix type tablets; since they can be widely distributed throughout the GI tract and produce local high concentration of drug at the absorption site. Therefore, it may be concluded that drug loaded floating microballoons are a suitable delivery system for

metformin with a new choice of an economical, safe and more bioavailable formulation in the management of type II diabetes mellitus.

ACKNOWLEDGEMENTS

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