Abstract

The microspheres have been utilized to obtain prolonged and uniform release in the stomach for development of once daily a formulation. The major advantage of the preparation technique includes, Short processing time, The lack of exposure of the ingredients to high temperature, High encapsulation efficiencies. From the literature review it was known that even though by changing the method of preparation, solvent composition and processing medium, the drug entrapment efficiency was found to be low in microspheres. The objective of the present investigation was to formulate and evaluate the microencapsulated controlled release preparations of metformin using ethyl cellulose as the retardant material with high entrapment efficiency and extended release. The formulated metformin loaded microspheres by solvent evaporation method by using aqueous medium as processing and tried to evaluate them for various in vitro characterization parameters.

Keywords: Metformin, Ethyl cellulose, Microspheres, Solvent evaporation.

Introduction: The concept of the advanced drug delivery systems especially those offering a sustained and controlled action of drug to desired area of effect, attained great appeal for nearly half a century. However, prior to advent of improved alternate methods, drug delivery systems were considered only as a means of getting the drug into the patient’s body. Actual practice of controlled release began with advent of timed release coating to the pills or solid drug particles in order to mask their unacceptable taste or make them more palatable. Between 1940s and 1960s, the concept of chemical microencapsulation technology began as on alternative means of delivering drugs. In continued quest for the more refined system, in 1980s polymer/membrane technology came to be known at for
front. Further, the process of targeting and site specific delivery with absolute accuracy can be achieved by attaching bioactive molecule to liposome’s, bio erodible polymer, implants, monoclonal antibodies and various particulate carriers (E.g., nanoparticles and microspheres, etc.). the micro particulate delivery systems are considered and accepted as a reliable means to deliver the drug to the target site with specificity, if modified, and to maintain the desired concentration at the site of interest without untoward effect(s). The term microcapsule, is defined as a spherical particle with size varying from 50nm to 2mm, containing a core substance. Microspheres are, in strict sense, spherical empty particles.

However, the terms microcapsules and microspheres are often used synonymously. In addition, some related terms are used as well. For example, essentially “micro beads” and “beads” are used alternatively. Spheres and spherical particles are also used for a large size and rigid morphology. The microsphere are characteristically free flowing powers consisting of proteins or synthetic polymers, which are biodegradable in nature, and ideally having a particle size less than 100 mm. Solid biodegradable microspheres incorporating a drug dispersed or dissolved throughout particle matrix have the potential for the controlled release of drug. These carriers received much attention not only for prolonged release but also for the targeting of the anticancer drugs to the tumor.

The micro spheres can be prepared by using any of the several techniques discussed in the following sections, (Rajeev jain 2000) but the choice of the technique mainly depends on the nature of the polymer used, the drug, the intended use and the duration of therapy. Moreover, the method of preparation and its choice are equivocally determined by some formulation and technology related factors as mentioned below: The particle size requirement. The drug or the protein should not be adversely affected by the process. Reproducibility of the release profile and method. No stability problem they should be non toxic product(s) associated with the final product.

Synthetic polymers are now material of choice for the controlled release as well as targeted micro particulate carriers. The initial work was carried out on the non-biodegradable polymers but later on, the interest has been shifted to the biodegradable polymers. Different types of methods are employed for the preparation of the
microspheres. These include in situ polymerization, solvent evaporation, coacervation phase separation, spray drying and spray congealing, etc.

**Controlled drug delivery:**

Controlled drug delivery occurs when a polymer, whether natural or synthetic, is judiciously combined with a drug or other active agent in such a way that the active agent is released from the material in a predesigned manner. The release of the active agent may be constant over a long period, it may be cyclic over a long period, or it may be triggered by the environment or other external events. In any case, the purpose behind controlling the drug delivery is to achieve more effective therapies while eliminating the potential for both under- and overdosing. Other advantages of using controlled-delivery systems can include the maintenance of drug levels within a desired range, the need for fewer administrations, optimal use of the drug in question, and increased patient compliance. While these advantages can be significant, the potential disadvantages cannot be ignored: the possible toxicity or non biocompatibility of the materials used, undesirable by-products of degradation, any surgery required to implant or remove the system, the chance of patient discomfort from the delivery device, and the higher cost of controlled-release systems compared with traditional pharmaceutical formulations.

Providing control over the drug delivery can be the most important factor at times when traditional oral or injectable drug formulations cannot be used. These include situations requiring the slow release of water-soluble drugs, the fast release of low-solubility drugs, drug delivery to specific sites, drug delivery using nano particulate systems, delivery of two or more agents with the same formulation, and systems based on carriers that can dissolve or degrade and be readily eliminated. The ideal drug delivery system should be inert, biocompatible, mechanically strong, comfortable for the patient, capable of achieving high drug loading, safe from accidental release, simple to administer and remove, and easy to fabricate and sterilize.

The goal of many of the original controlled-release systems was to achieve a delivery profile that would yield a high blood level of the drug over a long period of time. With traditional tablets or injections, the drug level in the blood follows the profile shown in Figure 1a, in which the level rises after each administration of the drug
and then decreases until the next administration. The key point with traditional drug administration is that the blood level of the agent should remain between a maximum value, which may represent a toxic level, and a minimum value, below which the drug is no longer effective. In controlled drug delivery systems designed for long-term administration, the drug level in the blood follows the profile shown in Figure 1b, remaining constant, between the desired maximum and minimum, for an extended period of time.

In recent years, controlled drug delivery formulations and the polymers used in these systems have become much more sophisticated, with the ability to do more than simply extend the effective release period for a particular drug. For example, current controlled-release systems can respond to changes in the biological environment and deliver—or cease to deliver—drugs based on these changes. In addition, materials have been developed that should lead to targeted delivery systems, in which a particular formulation can be directed to the specific cell, tissue, or site where the drug it contains is to be delivered. While much of this work is still in its early stages, emerging technologies offer possibilities that scientists have only begun to explore.

**CONTROLLED-RELEASE MECHANISMS:**

**Figure 1a, 1b: Drug delivery from a typical matrix drug delivery system.**

There are three primary mechanisms by which active agents can be released from a delivery system: diffusion, degradation, and swelling followed by diffusion. Any or all of these mechanisms may occur in a given release system. Diffusion occurs when a drug or other active agent passes through the polymer that forms the controlled-release device. The diffusion can occur on a macroscopic scale—as through pores in the polymer
matrix—or on a molecular level, by passing between polymer chains. Examples of diffusion-release systems are shown in Figures 1.

In Figure 1, a polymer and active agent have been mixed to form a homogeneous system, also referred to as a matrix system. Diffusion occurs when the drug passes from the polymer matrix into the external environment. As the release continues, its rate normally decreases with this type of system, since the active agent has a progressively longer distance to travel and therefore requires a longer diffusion time to release.

For the reservoir systems shown in Figures 1a and 1b, the drug delivery rate can remain fairly constant. In this design, a reservoir—whether solid drug, dilute solution, or highly concentrated drug solution within a polymer matrix—is surrounded by a film or membrane of a rate-controlling material. The only structure effectively limiting the release of the drug is the polymer layer surrounding the reservoir. Since this polymer coating is essentially uniform and of a no changing thickness, the diffusion rate of the active agent can be kept fairly stable throughout the lifetime of the delivery system. The system shown in Figure 1a is representative of an implantable or oral reservoir delivery system, whereas the system shown in Figure 1b illustrates Transdermal drug delivery system, in which only one side of the device will actually be delivering the drug.

**Biomaterials for delivery systems:**

A range of materials have been employed to control the release of drugs and other active agents. The earliest of these polymers were originally intended for other, non biological uses, and were selected because of their desirable physical properties, for example: Poly(urethanes) for elasticity. Poly(siloxanes) or silicones for insulating ability. Poly(methyl methacrylate) for physical strength and transparency. Poly(vinyl alcohol) for hydrophilicity and strength. Poly(ethylene) for toughness and lack of swelling. Poly(vinyl pyrrolidine) for suspension capabilities.

To be successfully used in controlled drug delivery formulations, a material must be chemically inert and free of leachable impurities. It must also have an appropriate physical structure, with minimal undesired aging, and be readily processable. Some of the materials that are currently being used or studied for controlled drug delivery
include: Poly(2-hydroxy ethyl Mehta cry late). Poly(N-vinyl pyrrolidine). Poly(methyl methacrylate). Poly(vinyl alcohol). Poly(acrylic acid). Polyacrylamide. Poly(ethylene-co-vinyl acetate). Poly(ethylene glycol). Poly(methyl acrylic acid). However, in recent years additional polymers designed primarily for medical applications have entered the arena of controlled release. Many of these materials are designed to degrade within the body, among them: Polylactides (PLA). Polyglycolides (PGA). Poly (lactide-co-glycolides) (PLGA). Poly anhydrides. Poly orthoesters. Originally, polylactides and polyglycolides were used as absorbable suture material, and it was a natural step to work with these polymers in controlled drug delivery systems. The greatest advantage of these degradable polymers is that they are broken down into biologically acceptable molecules that are metabolized and removed from the body via normal metabolic pathways. However, biodegradable materials do produce degradation by-products that must be tolerated with little or no adverse reactions within the biological environment. These degradation products—both desirable and potentially non desirable—must be tested thoroughly, since there are a number of factors that will affect the biodegradation of the original materials. The most important of these factors are shown in the box below—a list that is by no means complete, but does provide an indication of the breadth of structural, chemical, and processing properties that can affect biodegradable delivery systems. **FACTORS AFFECTING Biodegradation of polymers:**

Metformin hydrochloride:
Metformin (Trade names Glucophage, Diabex, Diaformin, Fortamet, Riomet, Glumetza and others) is an anti-diabetic drugs from the biguanide class of oral anihyperglycemic agents. Other biguanides include the withdrawn agents phenformin and buformin, Metformin is the most popular anti-diabetic drug in the United States and one of the most prescribed drugs overall, with nearly 35 million prescriptions filled in 2006 for generic metformin alone[1].

Metformin hydrochloride is a white to off-white crystalline compound with a molecular formula of C₄H₁₁N₅ . HCl and a molecular weight of 165.63. Metformin hydrochloride is freely soluble in water and is practically insoluble in acetone ether, and chloroform. The pKₐ of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68. IUPAC name:1-(di amino methylidine)-3,3-di methyl-guanidine. Chemical formula: C₄H₁₁N₅.

Bioavailability: 50 to 60% under fasting conditions. Half life: 6.2 hours. Excretion: Active renal tubular excretion by OCT₂.

Mechanism of action:
The exact mechanism of action of metformin is uncertain despite its known therapeutic benefits. Its mode of action appears to be reduction of hepatic gluconeogenesis, decreased absorption of glucose from the gastrointestinal tract, and increased insulin sensitivity. The 'average' person with type 2 diabetes has three times the normal rate of gluconeogenesis; metformin treatment reduces this by over one third .It has also been shown to decrease intestinal absorption of glucose, and may also improve insulin sensitivity by increasing peripheral glucose uptake and
utilization, although such an effect will occur nonspecifically following the lowering of glucose levels, regardless of how this lowering was achieved. A 2001 study showed that metformin stimulates the hepatic enzyme AMP activated protein kinase (AMPK), which plays an important role in the metabolism of fats and glucose.

Formulations:
To formulate eight metformin loaded ethyl cellulose microspheres with different Polymer to drug ratio, volume of processing medium and Stirring speed, Polymer: drug Ratio (0.5:1, 1:1, 1.5:1, 2:1). Volume of processing medium (100 ml), Stirring speed (500 and 900rpm). Microspheres were prepared by solvent evaporation technique using Ethyl cellulose as the rate controlling polymer and 300mg of metformin hydrochloride per batch and its in vitro evaluation tests like The particle size & distribution, % yield Entrapment efficiency, scanning electron microscopy (SEM), Infrared spectroscopy (IR), Differential scanning calorimetry (DSC), In vitro drug release behavior (Dissolution studies).

Materials and Methods:
Metformin hydrochloride (anti diabetic drug), Ethyl cellulose (7cps), Acetone and n-hexane, Processing medium (Distilled water.)

Metformin hydrochloride was obtained as a gift sample from Natco pharma Ltd (Hyderabad, India). Ethyl cellulose (7cps) was obtained from central drug house (Mumbai, India). All other chemicals were of analytical grade and were used as procured.

Metformin hydrochloride, the anti-diabetic drug approved for clinical use, is still widely used for treatment of diabetes. Metformin is typically administered orally as a capsule. This drug has a very short half life of 6 hours and has low oral bioavailability (60%) due to considerable first pass metabolism, thus necessitating frequent administration of large doses (1.5-2.0 g/day) to maintain therapeutic drug levels and high incidence of GI effects (30% cases). 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. So for this reason Metformin hydrochloride requires controlled release.

**Ethyl cellulose (7cps):**

Ethyl cellulose, being a biocompatible, non-biodegradable and one of the extensively studied encapsulating materials for the controlled release of pharmaceuticals (Chowdary et al. 2004), was used as the retardant material. Complete evaporation of the organic solvent had taken place. That is about 60mins. After 1hr, 10ml of n-hexane was added to harden the microspheres and the stirring was continued for another 30mins. Finally the harden microspheres were collected by filtration and washed with three portions of 50ml of n-hexane and air dried over night at room temperature. Each formulation was prepared at least twice, and the resulting batches were combined. The characterization of the microspheres was carried out on pooled batches.

**Preparation method:**

8 formulations of microspheres were prepared by solvent evaporation method, using different ratios of ethyl cellulose to metformin ratio. Ethyl cellulose (150mg) and metformin (300mg) that is 0.5:1(P:D) ratio were dissolved in 6 ml of mixed solvent system (organic phase) consisting of Acetone and n-hexane in a 1:0.5 ratio. The aqueous phase was 50 ml of water and which is pre saturated with Metformin hydrochloride (30 mg/ml). The organic phase was poured in to the aqueous phase and stirred at approximately 500 rpm to form an emulsion. The emulsion was stirred at the same speed, at room temperature, until the microspheres and the stirring was continued for another 30mins. Finally the harden microspheres were collected by filtration and washed with three portions of 50ml of n-hexane and air dried over night at room temperature.[16,17]

**Size distribution of microspheres:**

Microspheres were separated into different size fractions by sieving for 10 min using a Mechanical shaker (geologists Syndicate pvt Ltd, India) containing standard sieves having Apertures of 710, 500, 355, 250,125, 80, 60, 45, 30 and 20 mm (Indian Pharmacopoeia 1996). The particle size distribution of the microspheres for all the
formulations was determined and mean particle size of microspheres was calculated by using the following formula.

\[
\text{Mean particle size} = \frac{\sum (\text{mean particle size of the fraction} \times \text{weight fraction})}{\sum (\text{weight fraction})}
\]

**Drug entrapment efficiency:**

The amount of Metformin present in the microspheres was determined by extracting into phosphate buffer (pH 7.4). Microspheres were crushed and powdered by using a mortar and pestle and accurately weighed amount of this powder was extracted into 100ml of phosphate buffer (pH 7.4) by stirring at 900 rpm for 2 h. The solution was filtered; suitable dilutions were made and estimated for Metformin content spectrophotometrically at 233 nm.

**Scanning electron microscopy (SEM):**

The samples for the SEM analysis were prepared by sprinkling the microspheres on one side of a double adhesive stub. The stub was then coated with gold (Fine coat, Ion sputter, JFC-1100). The microspheres were then observed with the scanning electron microscope (JEOL, JSM-6360, scanning electron microscope, Japan) at 15 kv. The samples include blank microspheres, drug loaded microspheres.

**Infrared spectroscopy:**

Infrared spectra of Metformin, ethyl cellulose blank microspheres and Metformin loaded microspheres taken by using KBr pellet technique and were recorded on a Perkin Elmer-883 infrared spectrophotometer.

**Differential scanning calorimetry:**

Differential scanning calorimetry (DSC) scans of Metformin and blank and drug loaded microspheres were performed using Universal V 2.5H DSC model. The analysis was performed with a heating range of 25–250°C and at a rate of 10°Cmin⁻¹.

**In vitro release studies:**

Dissolution testing over the last quarter century has emerged as a highly valuable in vitro test to characterize drug product performance. For the test to be useful, it should be simple, reliable and reproducible.
and should be able to discriminate between different degrees of product performance. The value of the test is significantly enhanced when product performance is evaluated as a function of time, i.e., when the dissolution profile is determined rather than a single point determination, which is a standard compendia for batch release. [2-6]

Dissolution tests are used to assess batch to batch quality, where the approach forms the basis for specifications (test, methodology, acceptance criteria) to allow batch release. Dissolution is also used to: 1) provide process control and quality assurance; and 2) assess the need for further bioequivalence (BE) studies relative to minor post-approval changes, where it can function as a signal of bioequivalence. [7-15] In vitro dissolution studies for all product formulations investigated (including prototype formulations) are encouraged, particularly if in vivo absorption characteristics are being defined for the different product formulations. Such efforts may allow an in vitro/in vivo correlation. When an in vitro correlation or association is available, the in vitro test can serve not only as a quality control specification for the manufacturing process, but also as an indicator of how the product will perform in vivo. Dissolution guidance’s developed by the Agency provide recommendations on the development of dissolution test methodology, on how to set specifications for dissolution testing, and the regulatory applications of dissolution testing. Recent draft FDA guidance based on the bio pharmaceutics classification system suggests that documentation of bioequivalence via dissolution studies may be appropriate for orally administered immediate release drug products which are highly soluble, highly permeable and rapidly dissolving.[18-22]

A dissolution profile or at least a two-point determination should be used to characterize the in vitro performance of an immediate release drug product. Because a modified release dosage form is a more complex formulation, three to four dissolution time points are needed to characterize the product. Dissolution profile comparison has been extensively used in assessing product sameness, especially in the presence of certain SUPAC related post-approval changes. In order to avoid subjective evaluation of dissolution profile comparison, FDA has adopted a simple method to compare dissolution profiles, which is termed a similarity factor.
The in vitro release studies of drug loaded microspheres were carried out at 37°C and 100 rpm using phosphate buffer pH 7.4 (500 ml) in USP dissolution apparatus under sink conditions. Accurately weighed samples of microspheres (size fraction 355 mm) were added to dissolution medium and, at pre-set time intervals, 5ml aliquots are withdrawn and replaced by an equal volume of fresh dissolution medium. After suitable dilution, the samples were analyzed spectrophotometrically at 233 nm. The concentration of Metformin in test samples was corrected and calculated using a regression equation of the calibration curve.[23-26]

Results and Discussion:

Metformin hydrochloride due to its hydrophilicity is likely to preferentially partition out into the aqueous medium, leading to low entrapment efficiency, when encapsulated using the aqueous phase as the processing medium (Mandal et al. 1996). Depending on the processing conditions, as much as 80% of the Metformin can partition out into the outer processing medium (Mandal et al. 1996). To avoid the loss of this water soluble drug from internal phase the aqueous phase was pre saturated with Metformin (30mg/mL), which improves the loading efficiency.

Preparation of microspheres:

Microspheres were prepared by emulsion solvent evaporation method. The preparation of microspheres was carried out by emulsifying an aqueous solution into a solution of drug and polymer in mixed solvent system comprising of Acetone and n-hexane in1:0.5 ratios. Microspheres were formed after a series of steps like solvent extraction and solvent evaporation. The solvents of the system were removed by a combination of extraction and evaporation. It is very important to carefully select the solvent combination and processing medium to enable the formation of emulsion and solvent extraction and evaporation by a combination.

Acetone is a unique organic solvent which is polar, water miscible and oil immiscible and n- hexane is non solvent for polymer during the formation of microspheres, Acetone and n-hexane was evaporated during stirring. Each step of microsphere preparation was keenly observed to understand the effect on the particle size, total entrapment and release profiles of the drug loaded microspheres. After introduction of emulsion into external aqueous phase, the Emulsion was stirred for 2 hours using a mechanical stirrer, during this phase it is assumed that
the droplet sizes were allowed to stabilize while some amount of n-hexane and acetone escaped, making the emulsion droplets become more viscous.

The n-hexane, non-solvent for the polymer added at this stage might have caused the quick precipitation of the polymer leaving the surface of microspheres porous. No surfactant was used for stabilizing the emulsion, since ethyl cellulose has the additional property of stabilizing o/w emulsion (Melzer et al. 2003). The process and formulation parameters, of which some were kept constant after optimization of the process, and others were varied to study the effect on mean particle size (given in Table).

**Scanning electron microscopy (SEM):**

As shown in SEM photographs (Figure 2), the microspheres were spherical and porous. The surface of the microspheres was rough and revealed the presence of pores both in the blank and drug loaded microspheres. The study of drug loaded microspheres showed the presence of drug particles on the surface, which was responsible for the initial burst release of the drug during dissolution. Surface study of the microspheres after dissolution showed bigger pores, suggesting that the drug was released through pores and the mechanism of drug release may be diffusion controlled. An incident electron beam is raster-scanned across the sample's surface, and the resulting electrons emitted from the sample are collected to form an image of the surface. Imaging is typically obtained using secondary electrons for the best resolution of fine surface topographical features. Alternatively, imaging with backscattered electrons gives contrast based on atomic number to resolve microscopic composition variations, as well as, topographical information. Qualitative and quantitative chemical analysis information is also obtained using an energy dispersive x-ray spectrometer with the SEM. Scanning electron micrographs of Metformin loaded and blank microspheres are shown in the following figure.2

**Infrared spectroscopy:**

The infrared spectra of Metformin and Metformin loaded microspheres were comparable and the peaks of Metformin loaded microspheres are of lower intensity than the pure drug. No drug polymer incompatibility was
noted in their FTIR spectra. spectra's of pure drug, drug loaded spheres and ethyl cellulose microspheres were shown in the following figures.3a,3b

**Differential scanning calorimetry:**

Differential scanning calorimetry (DSC) of Metformin showed a sharp endothermic peak that corresponds to melting in the range of 225–235°C (Araujo et al. 2003), as shown in Figure 1. Metformin in the ethyl cellulose microspheres also showed a similar characteristic peak with decreased intensity showing its stability during the encapsulation process. Fig No 4a, 4b, 4c

**The particle size and distribution:**

The mean particle sizes (microns) and distribution of the formulated microspheres are listed in the table. The mean particle sizes of the microspheres were increased as the polymer to drug ratio increases. By increasing the stirring speed from 500rpm to 900rpm and increasing the volume of the processing medium from 100ml decreased particle size of the microspheres were reported. By this one can concludes that the mean particle size of the microspheres depends on polymer-drug ratio, stirring speed and volume of processing medium. By increasing the stirring speed and volume of the processing medium one can able to reduce the mean particle size the microspheres.

<table>
<thead>
<tr>
<th>Batch</th>
<th>Formulation number</th>
<th>Polymer: Drug ratio (mg)</th>
<th>Volume of external phase (ml)</th>
<th>Stirring speed (rpm)</th>
<th>Mean particle size (microns)</th>
<th>Yield (%)</th>
<th>Entrapment efficiency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A 1</td>
<td>150:300(0.5:1)</td>
<td>100</td>
<td>500</td>
<td>100</td>
<td>87.1</td>
<td>48.04</td>
<td></td>
</tr>
<tr>
<td>A 2</td>
<td>150:300(0.5:1)</td>
<td>100</td>
<td>900</td>
<td>80</td>
<td>89.3</td>
<td>39.03</td>
<td></td>
</tr>
<tr>
<td>B 3</td>
<td>300:300(1:1)</td>
<td>100</td>
<td>500</td>
<td>200</td>
<td>88.6</td>
<td>51.03</td>
<td></td>
</tr>
<tr>
<td>B 4</td>
<td>300:300(1:1)</td>
<td>100</td>
<td>900</td>
<td>150</td>
<td>94.5</td>
<td>46.06</td>
<td></td>
</tr>
<tr>
<td>C 5</td>
<td>450:300(0.5:1)</td>
<td>100</td>
<td>500</td>
<td>500</td>
<td>94.6</td>
<td>65.16</td>
<td></td>
</tr>
<tr>
<td>C 6</td>
<td>450:300(0.5:1)</td>
<td>100</td>
<td>900</td>
<td>355</td>
<td>95.3</td>
<td>57.64</td>
<td></td>
</tr>
<tr>
<td>D 7</td>
<td>600:300(2:1)</td>
<td>100</td>
<td>500</td>
<td>710</td>
<td>91.6</td>
<td>72.07</td>
<td></td>
</tr>
<tr>
<td>D 8</td>
<td>600:300(2:1)</td>
<td>100</td>
<td>900</td>
<td>500</td>
<td>93.0</td>
<td>69.06</td>
<td></td>
</tr>
</tbody>
</table>
Yield and entrapment efficiency:

The yield and entrapment efficiency of drug loaded microspheres of different polymer to drug ratios are shown in table. Entrapment efficiency of the drug was increased as the polymer to drug ratio increase and dependent on its solubility in the solvents and processing medium and also depends on the physicochemical properties of the drug and polymer. The entrapment efficiency of the drug was in the range of 39.03 - 72.07%. The less entrapment efficiency than expected may be because of high solubility of the drug in the mixed solvent system comprising of Acetone and n-hexane, due to its high solubility, the drug may be migrated to processing medium during extraction and evaporation processes of n-hexane and Acetone respectively. This assumption was supported by SEM analysis, which showed the presence of drug particles on the surface of the microspheres revealing the migration phenomena of the drug to the processing medium.

In vitro release studies:

The in vitro release of metformin from ethyl cellulose microspheres was biphasic with the initial burst effect, which was varied from 20–70% depending on the polymer-to-drug ratio. The initial burst effect was due to the presence of drug particles on the surface of the microspheres, which was revealed by SEM studies. The initial burst effect may be attributed as a desired effect to ensure initial high plasma concentrations of drug to elicit pharmacological activity. In order to keep the total surface area of the microspheres constant and, thus, to get comparable results, the release studies were carried out with 250 mm size fractions.

The release profiles are shown in Figure. The effect of retardation on the release rate depends on the polymer-to-drug ratio. As the concentration of ethyl cellulose increased with respect to drug concentration, the release rate was decreased which may be attributed to the slower rate of diffusion of dissolution medium into the microspheres due to increased thickness of the polymer matrix. As ethyl cellulose concentration increased, the drug release was extended up to 12–16 hours. The release profile of metformin microspheres were compared with that of the two marketed products such as Bigomet SR(Ranbaxy),Azulix(Torrent).the results were shown in the following table.
Table:

<table>
<thead>
<tr>
<th>TIME</th>
<th>% release of bigomet SR</th>
<th>% release of azulix</th>
<th>% release of metformin microspheres</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>32</td>
<td>33</td>
<td>26</td>
</tr>
<tr>
<td>2</td>
<td>45</td>
<td>41</td>
<td>34</td>
</tr>
<tr>
<td>4</td>
<td>58</td>
<td>55</td>
<td>46</td>
</tr>
<tr>
<td>6</td>
<td>78</td>
<td>74</td>
<td>62</td>
</tr>
<tr>
<td>8</td>
<td>86</td>
<td>84</td>
<td>72</td>
</tr>
<tr>
<td>10</td>
<td>90</td>
<td>91</td>
<td>80</td>
</tr>
<tr>
<td>12</td>
<td>96</td>
<td>97</td>
<td>91</td>
</tr>
</tbody>
</table>

Fig 2: Comparative study of metformin microspheres with two marketed products.
Summary and Conclusion: The microspheres have been utilized to obtain prolonged and uniform release in the stomach for development of a once daily formulation. The major advantage of the preparation technique includes: Short processing time, The lack of exposure of the ingredients to high temperature, High encapsulation efficiencies. In the present study, preparation of metformin hydrochloride microspheres, evaluation of Drug Delivery System (DDS) in vitro, prediction of the release, and drug release pattern to match target release profile was investigated. microspheres were prepared by solvent evaporation technique using Ethyl cellulose as the rate controlling polymer and 300 mg of metformin hydrochloride per batch and its in vitro performance was evaluated by the usual pharmacopoeia and other tests such as, Drug polymer compatibility (FTIR scan),Yield (%),Particle size analysis, Drug entrapment efficiency, Surface topography, In vitro release studies. Where the polymer ratio increases, the particle size may also increases, thus entrapment efficiency increases, hence the release profile was extended. As rotation speed increases, the particle size will decrease, they are inversely proportional to each other. The developed microspheres of metformin hydrochloride may be used in clinical for prolonged drug release in stomach for at least 12 hrs, thereby improving the bioavailability and patient compliance.

The experimental design supported product development and procedure yielded the desired microspheres with drug release equivalent to those of the marketed single unit dosage forms. The optimized metformin HCl delivery system is expected to provide clinicians with a new choice of an economical, safe and more bio available formulation in the management of type II diabetes mellitus. Therefore, it may be concluded that drug loaded floating microspheres are a suitable delivery system for metformin hydrochloride, and may be used for effective management of NIDDM.

References:


Corresponding Author:
KishoreKumar ReddyK*,
Email:kishorereddy47@yahoo.co.in