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Recent Advancement of Designing and Characterization for Stomach Specific Muco-Adhesive Microspheres

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Abstract:

The Present Review Article is prepared as comprehensive research article for gastro retentive microspheres. It covers basic anatomy and physiology of stomach and lists different merit and demerit for gastro retentive muco-adhesive systems. It specially emphasizes about factor affecting gastric retention, selection of suitable drug, discussion of different approaches for gastric retention and different method for preparation of muco adhesive microspheres. The current review article also focus on characterization of microspheres.

Keyword : *Gastric Retention, Muco Adhesion , Microspheres*

1. Introduction

1.1 Gastro-retentive Drug Delivery System (GRDDS)

Oral controlled drug delivery (OCDDS) has lot of advantages over conventional drug delivery systems like eases of administration of formulations, patient's compliances and flexibility in pharmaceutical formulations[1]. Along with advantages of oral controlled drug delivery systems, there are also some drawbacks such as specificity of drug release in gastro-intestinal tract of patient body because of human gastro-intestinal tract (GIT) has variable gastric motility behaviour[2, 3]. In human begins , stomach has emptying time about two-three hours during which dosage form can release drug from formulation into stomach, usually drug release from formulation in controlled manner. But after 2- hours, dosage form may leaves the stomach and moves to next gastro-intestinal regions such as small intestine, large intestine etc[4]. Hence, once dosage form leaves the major absorption zone i.e. stomach or upper gastrointestinal tract, it could result in loss of drug and poor patient's drug therapy as drug could not achieve a required therapeutic concentration[5]. Therefore to overcome this drawback of oral controlled drug delivery systems, there is need of development of targeting delivery systems[6].

Gastro-retentive drug delivery systems could overcome the major drawback of oral control drug delivery system[7]. This systems retain drug formulations within stomach or upper gastro-retentive and release the drug in controlled fashion for prolong period of time about 12 hours[3]. This could result in enhance in drug

absorption and improvement in bio-availability. Gastro-retentive systems are mostly useful for treatment of stomach and proximal small intestine. It is also useful to improve pharmacokinetics and pharmaco-dynamic problems of drugs[8]. There are several mechanisms in which gastro-retentive drug delivery systems works.

- By incorporation of low density polymers into pharmaceutical formulation. [9]
- Using high density polymer may used so that formulation gets settle down at the lower part of stomach.[10, 11]
- By using muco-adhesive polymer , formulation could adheres to stomach mucosa and retain for longer period of time.[12, 13]
- Some time it slow down gastro-intestinal tract motility by using co-administration of drug.[14, 15]
- Expanding and swelling polymer may useful it gastro-retentive drug delivery systems as these polymer increases in size to many fold time so that drug formulation could not leave the stomach until it breaks downs into smaller fragment.[16, 17]

1.2 Basic Anatomy of Stomach and Its Physiology

Devis who first time coins term - floating drug delivery in pharmaceutical research area.[18]. For designed and development of gastro-retentive drug delivery systems, it is desirable to review the anatomy physiological function of human stomach.[19, 20]. At rest, before meal human stomach has capacity about 25-50 ml which may expand up to 1200-1500 ml after feeding[21]. As per consult of anatomy of stomach, it is located in region of just bellow diaphragm and left side of abdominal region[14]. It has a shape above like's English alphabetical "J" shape[22]. The stomach is responsible for to store food for short time period of time during which food is continuously grinding and after reduction of its size it moves to next gastro-intestinal region such as duodenal[14, 22]. The most of active ingredients (drug) of pharmaceutical dosage formulation are absorb from stomach, therefore GRDDS may beneficial for this type of drugs[22].

Figure No 1 illustrated that the human stomach is divided into following three major regions such as:-

I. **Fundus :**

It acts as reservoirs for food as it receive it from oesophagus; it also called as proximal stomach[23, 24].

II. **Body :**

It is area where food being processing such as gridding and various physiological process. It makes the food ready for digestion[23, 24].

III. **Pylorus or Antrum (Distal Stomach):**

It acts as mixing site and hold large particle to be preceding size reduction and allow passing small particle to move through pyloric sphincters[23, 24].

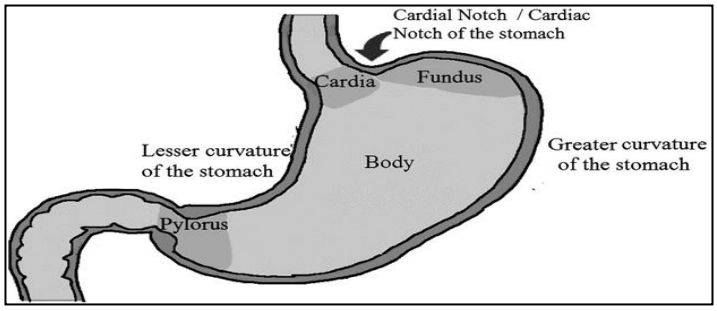

Figure No 1. Anatomy of the Stomach[25]

1.3 Gastric Motility:

For successful development GRDDS, sufficient knowledge of gastric emptying is needed. Gastric motility is divided into four major stage /phase[23, 24].

a. **Phase I (Quiescent Period) :**

It has low amplitude of contraction. It is lasting for about 30-80 minutes[23, 24]..

b. **Phase II**:

It has intermits amplitude of contractions (between phase 1 and phase 3). During contraction period, bile is continuously secretes. It is lasting for about 1 -50 min[23, 24].

c. Phase 3 (House Keeping Wave):

It shows highest amplitude of contraction than other phases. The high amplitude contraction is responsible for maximum pyloric opening so that remaining food is completely evacuated from stomach and allows passing to next GI region[23, 24].

d. Phase 4:

It is intermediate stage /phase between phase 3 and phase 1. It shows shorter period of amplitude of contraction just about 4-8 min[23, 24].

In feeding stage gastric motility of stomach is induces after 6-10 min the feeding and remain for prolong period of time up to till food completely evacuated from stomach[23, 24].

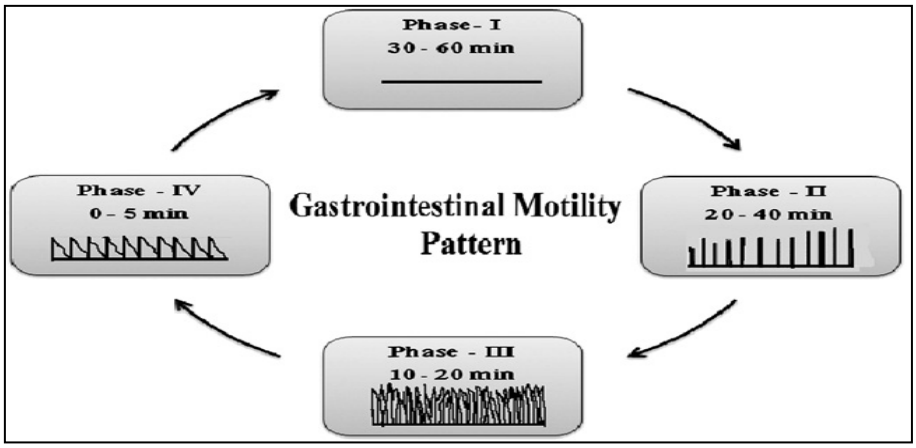

Figure No 2: Schematic Representation of Inter Digestive Gastric Motility Pattern[23, 24].

1.4

Need of Gastro-retentive Drug Delivery System

As per previous discussion(**1.1**), for traditional dosage form and controlled drug release formulation has disadvantages such as it unable to retain in absorption zone of a drug which may result in complete absorption of drug[26]. GRDDS is playing important role for such a drug which having narrow absorption zone in upper git region so that absorption of a drug may improve, ultimately it gives patient compliance for drug therapy[27]. The direct contact of absorption zone with a drug formulation for longer period of time, result in enhance absorption of drugs.[28] The most of OCDDS has first objective to release a drug in desirable GIT region up to 24 hours so that dosage regiment reduces [29]. Hence, GRDDS has been initiated for research and development in industry as well as academia to solve various problems of drug[30].

1.5 Advantage and Disadvantages of Gastro-retentive Drug Delivery Systems

1.5.1 Advantages (Merits)

Gastro-retentive drug delivery systems offer various advantages which are mentioned as follow:-

a) It improves the drug concentration in blood (bio-availability)[31-33].
b) It improves patience compliance by reducing dose regiments.[34].
c) It may use for local drug delivery for treatment of upper GTI aliment[35, 36].
d) It maintains plasma drug concentration within the desirable range and ultimately it improves drug therapy[37, 38].
e) It avoids GIT side effect.[39]

1.5.2 Disadvantage (Demerits) of GRDDS

Although GRDDS has advantage (Merits) as mentioned above but it also suffer from following disadvantages which are mentioned as bellowed:-

a) There is need to rise fluid level in stomach[31, 32]
b) It is a not suitable for various category of drug which has low solubility[33].
c) The absorption is limited for drug having absorption zone in lower GIT[34].
d) The muco-adhesive formulation may form strong covalent bond with stomach mucosa which is undesirable effect[40].
e) The feeding stage of stomach may interfere with gastro-retentive behaviours of dosage formulation[35, 37]
f) The body position of patients has also effect on gastro-retentive behaviours of dosage formulation[38].
g) Hydro-dynamically based swelling system takes prolong time to swell which may result in failure of gastro-retentive behaviours of formulation[39, 41].
h) It may disturbs the normal gastro-emptying behaviours if stomach[16].
i) Hydrosible and bio-degradable polymer may unstable or rapidly degrades which may result in failure of controlled release behaviours of GRDDS[42].

1.6 Factors Controlling Gastro-retentive Drug Delivery System

There are various factors which affect gastro-retentive drug delivery systems are summarised as follow:

1. **Density:** Low density is suitable for gastro-retentive behaviors of formulation[43-45].
2. **Size:** Size of dosage formulation more than 10mm is favorable[43-45].
3. **Shape:** Round and spherical shape is in favors of gastro-retentive behaviors[43-45].
4. **Single or multiple unit formulation:** It is need for better drug release profile[43-45].
5. **Fed or Unfed State:** Feed stage of stomach is desirable[43-45].
6. **Nature of Meal:** Fatty acid slow down gastric emptying time[43-45].
7. **Frequency of Feed:** Repeated feeding of stomach reduced gastric emptying time[43-45].
8. **Caloric Content:** Fatty acid and protein rich food prolong gastric emptying time to many fold time. [43-45].
9. **Gender:** Female has shorter gastro-retentive time than male[43-45].
10. **Age:** The 60 years old age patient have prolong gastro-emptying time[43-45].
11. **Posture:** It sows varies result[43-45].
12. **Disease State:** Diabetic, Chrohns disease may change physiology of stomach[43-45].

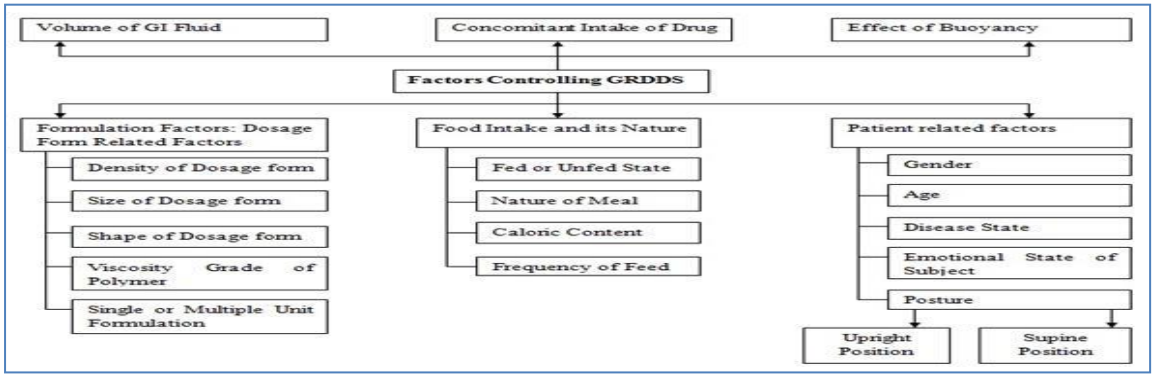

Figure No 3: Factors Controlling Gastro-retentive Drug Delivery System [46]

1.7 Drug Characteristics Required for Gastro-retentive Drug Delivery System

Ideal properties of drug for GRDDS as follow:

a) Drug which is specifically used for treatment of upper GIT[47].
b) Drug that degrade microbial flora of lower most region of GIT like colon[48].
c) Drug which has specially absorption pathway in upper GIT region[47].
d) Drug which do not show broad absorption pathway through GIT[27].
e) Drug which has better stability in lower pH range[49].

1.8 Drug which is not suitable for GRDDS has following properties:

a) Drug which is becomes rapidly destroys in acidic pH[50].
b) Drug which has restricted solubility behaviours in upper GIT[27].
c) Drug gets rapidly metabolise[51].
d) Drug which does not shows compatibility with biological tissue[52].

1.9 Approaches to Gastro-retentive Drug Delivery System.

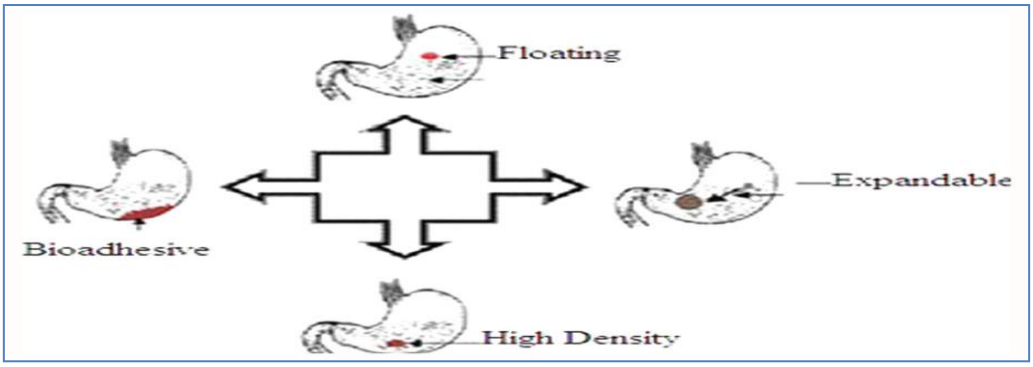

Figure No 4: Approaches to Gastro-retentive Drug Delivery System[53]

1.9.1 High-Density (Sinking) Systems

In this approach, sedimentation phenomenon has been utilizes so that drug formulation becomes sinks at the bottom of lower part of stomach. Also drug formulation could remain in stomach for prolong period[54].

1.9.2. Expandable Systems

In this approach, gastro-retentive formulations contain a swell able polymer which has capacity to swell up to 10 to 15 fold time than that of its original size[17]. Such formulations when comes in contact with gastro-intestinal fluid or stomach acidic environment, it becomes to swell which result in it could not remove from stomach until it breaks into small fragments. In this approach, gastro-retentive formulations could retain in stomach for 12 -24 hours.[52]

. **1.9.3. Super-Porous Hydrogel Systems**

In this approach, gastro-retentive formulation has small pore which having range in 100 um & it swells to equilibrium with in fraction of second when comes to contact with GI fluid.[55] Formulation becomes buoyant in stomach until its pore become equilibrium with pore size of mucosa[56]. During same time which drug release in slow manner from dosage form. In this approach, formulations could shows gastro-retentive behaviours up to 12-24 hours.

1.9.4. Muco-adhesive (Bio-Adhesive) Systems

In recent time muco-adhesive system is most popular in gastro-retentive drug delivery systems.[9] In this approach, formulation contains muco-adhesive polymers which could shows muco- adhesion with mucosa of stomach by various mechanisms[30]. Muco-adhesive formulation adheres to mucosa for prolong period of time and shows gastro-retentive behaviours[51]. Peristaltic movement of cilia of mucosa moves formulation towards downwards which is responsible for complete de –adhesion of formulation from mucosa.[57]. Both mechanisms have been going on simultaneously. In this approach muco-adhesion of formulation is about 12-14 hours[58].

1.9.5. Magnetic Systems

In this approach, gastro-retentive formulation contain small magnetic unit could be retain in stomach for prolong period of time until patient shows compliance [5, 30]. Gastro-retentive behaviours can be maintained by placing magnets on abdominal over position of stomach so that formulation should be retaining in stomach to improve gastro-retentive behaviours [58-61].

1.9.6. Low-Density (Floating) Systems

Amongst other approach, floating system has been widely utilizes for development of gastro-retentive formulation.[5, 62]. In this approach, formulation may contain low density polymers or gas generating agent [3, 20, 31, 63]. Formulations which utilize low density polymers could show buoyancy effect until it complexly degrades whereas formulations which utilizes gas generating agent also shows gastro-retentive behaviour until

entrapped gas or air completely remove and formulation become sink[63]. In both condition, formulation should have density below 1.004 g,/cm^2 for floating behaviours'[64-66] .

2 Muco-Adhesive Microspheres

In development of controlled drug delivery system, muco-adhesive microspheres have been achieved remarkable importance.[76] In last few decades, microspheres were prepared by using various bi-degradable polymers for control release but for specificity and targeting drug delivery, in recent years muco-adhesive polymer has much importance[67-70].

In development of gastro-retentive formulation, muco-adhesive is one of the choices for targeting, gastro-retentive, control drug release behaviours[71, 72]. Microspheres is small multi-particulate formulation which has about 1-1000 um in diameter. Core material such drug is coated by coating polymers which shows muco-adhesive behaviours in stomach.[73-75].

2.1 Advantages of Muco-adhesive Microspheres

a) Control drug release of muco-adhesive microspheres could maintains plasma drug concentration throughout treatment of disease[76-78].
b) It could improve compliance of patient for administration of formulation [18, 79, 80].
c) It reduced dosage frequency[18, 79, 80].
d) It enhances drug concentration in blood (Bio-availability) [18, 79, 80].
e) Spherical nature of formulation could be helpful for muco-adhesive and drug release [18, 79, 80].

2.2 Limitation of Muco-adhesive Microspheres

Some of the disadvantages were found to be as follows

a) It may show variables drug release pattern [18, 79, 80].
b) Release rate of drug from drug formulation may be modified by physiology and anatomy of stomach, diets, disease condition [18, 79, 80].
c) Release rate of drug may show variation as dose of formulation varies [18, 79, 80].
d) Patient should be instructed for proper administration of formulation [18, 79, 80].

2.3 Methods of Preparation of Muco-adhesive Microspheres

Muco-adhesive Microspheres can be prepared by using different techniques like:

2.3.1. Complex Co-acervation

In this method, core material which is to be coated by coating material is dissolved in insoluble solvent so that core material entrapped within matrix structure of coating material [81-83]. Phase separation coacervation method utilizes various approaches for separation core material or coating material for encapsulations such as pH change, temperature change, addition of salt, addition of incompatible polymer, polymer –polymer interaction [78, 84].

2.3.2. Hot Melt Microencapsulation

Microspheres can be prepared by hot melt technology which utilised following general method of preparation [85, 86]. Here, polymers are melted and drug and other excipients are add to melted polymer solution with continues stirring [5]. After that immiscible solution is add into polymeric solution for encapsulations of drug. Temperature of solution is allowed to cool down for solidification. The prepared microspheres are collected, washed, dried [87].

2.3.3. Emulsification-Internal Gelation Technique

In this method, polymer is dissolved in water and drug is added along with cross linking agent[88, 89]. The prepared polymeric solution is then added to mineral oil containing surfactant through needle[90, 91]. Microspheres are formed by emulsification–internal gelation method and it is collected, washed, and dried using suitable method.[92]

2.3.4. Double Emulsion Method

Ogowa Y (1998) has introduced this method[93]. In this method, primary emulsion is prepared by simple mixing drug & polymers into organic solvent. From primary emulsion, multiple emulsion or double emulsion is formed by adding primary emulsion base into excess aqueous quantity water which contain polymer and

emulsifying agents[94]. With the help of continuous stirring, organic solvent is evaporated leaving behind rigid microspheres. It is collected, washed, and dried using suitable method [95, 96].

2.3.5. Solvent Removal

In this method, water insoluble polymers are mixed with organic solvent and then drug along with cross linking agent is added [97, 98]. This solution is then added to oil phase which contain emulsifying agent by drop by drop using syringe. Petroleum ether is added to polymeric solution to extract organic solvent leaving behind microspheres. It collected, washed, and dried using suitable method[99].

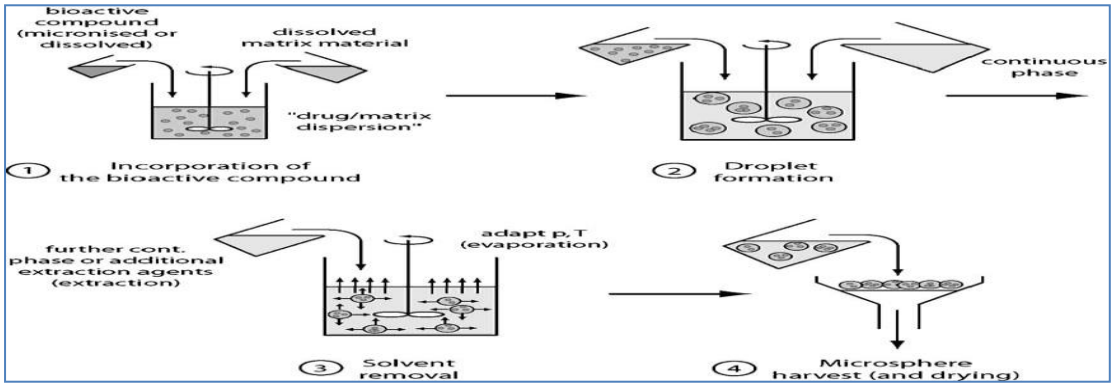

Figure No 5: Diagrammatic Presentation of Preparation of Microspheres by Solvent Removal[25]

2.3.6. *Iono-tropic* Gelation

In this method, polymers are completely dissolved in aqueous media and drug and polymer is added to calcium chloride solution with continues stirring. The microsphere are found to suspend on calcium chloride solution. It collected, washed, and dried using suitable method [93, 100, 101].

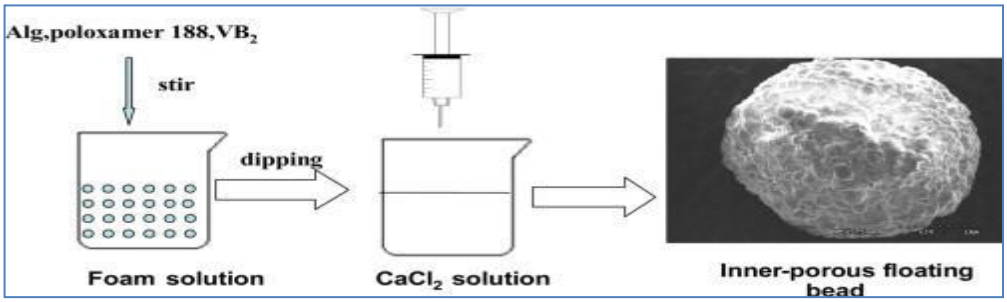

Figure No 6: Diagrammatic Presentation of Preparation of Microspheres by *Iono-Tropic* Gelation (A. Garg & Upadhyay, 2012)

2.3.7. Phase Inversion Method

In this method, polymer is added to organic solution and drug is added to it. This mixture is added to steady undisturbed non-organic solvent. It collected, washed, and dried using suitable method [93, 100, 101].

2.3.8. Spray Drying

In this method, polymeric mixture containing drug is sprayed into chamber of spray dryer [102] [103]. Due to high temperature of chamber, organic solvent evaporated and microsphere are formed and it is collected, washed, and dried using suitable method[104].

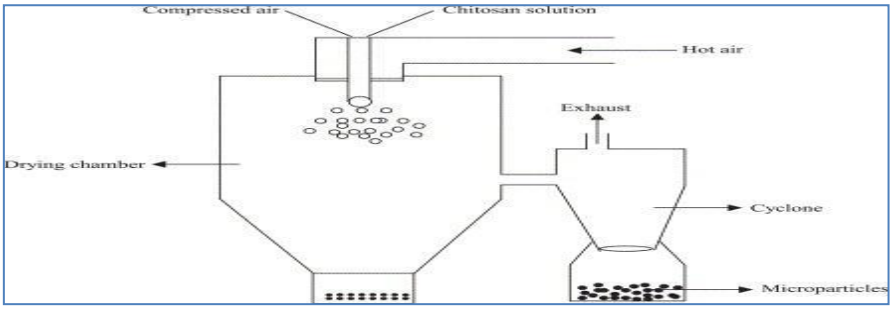

Figure No 7: Diagrammatic Presentation of Preparation of Microspheres by Spray Drying[93]

3. Evaluation of Muco-Adhesive Microspheres

3.1 Preformulation Studies

3.1.1. Drug-Polymers Interaction Study:-

The drug-polymers interaction study can be carried out by using FTIR spectrophotometer and Differential scanning calorimetry.

i) FTIR Spectroscopy:-

Drug, polymer under study and physical mixture of drug-polymers are filled in the pre-washed and dried ampoules and sealed. The sealed ampoules are kept at 37 ± 0.5°C for 28 days in stability. At the end of 28 days, the FTIR spectrum of drug polymer, physical mixture of drug-polymers are recorded on an Infrared spectrophotometer. IR spectrums can be recorded in the frequency range 400-4000 cm^{-1} **[105-107]**

ii) Differential Scanning Calorimeter Analysis:

Drug and physical mixture of drug and polymers are filled in the pre-washed and dried ampoules and sealed. The sealed ampoules were kept at 37 ± 0.5°C for 28 days in stability. At the end of 28 days, the thermograph can be obtained using Differential Scanning Calorimeter. A required of drug is weighted and it is placed in the sample crucible. Set the temperature range and the heating rate given on instruments control panel. DSC Thermographs for drug and physical mixture of drug-polymers are obtained with the temperature on the *x-axis* and the energy change on the *y-axis*. Note down the start of peaks, end of peaks, height of peaks, peak width, also glass temperature were note down if any from DSC thermographs of drug and physical mixture of drug-polymers **[105-107]**.

3.1.2. Calculation of Dose:

For controlled drug release up to 24 h, the total dose of drug require can be calculated based on the conventional dose of a drug. The total dose required can be calculated using the following equation [11, 108-110].

D_t = Dose $(1 + 0.693 \times t/t_{1/2})$

Hère

D_t = Total dose

Dose = Immediate release dose

t = Total time period for which controlled release is required

$t_{1/2}$ = Half life of drug

3.2 Characterization of Muco-Adhesive Microspheres

i) Percentage Yield:-

Percentage yield of muco-adhesive microspheres can be calculated by simple mathematical calculation. Total solid contain weight of drug and excipient is calculated and it is considered as theoretical yield of microspheres. Total weight of microsphere, after preparation of formulation batch is considered as actual weight of product. Experiments can be repeated to get precision & reproducibility [111, 112].

$$\% \text{ Yield} = \frac{\text{Actual weight of product}}{\text{Total weight of excipients and drug}} \times 100$$

ii) Particle Size Determination:-

Muco-adhesive microspheres size are determined by using optical microscopic method with the help of ocular and stage micrometer. The sizes of around 100 microspheres were measured and their average size was determined.

Experiments were performed in triplicate and average result with standard deviation is shown in result and discussion chapter of formulation batch Durrani, Davies, Thomas, & Kellaway, 1992).

iii) Drug Entrapment Efficiency:-

One gram of Muco-adhesive microspheres was taken for triturating in mortar-pestle. Powder blend equivalent to total weight of formulation was weighed and it was added to 250 ml breaker. Dissolution media such as 0.1N HCl having pH 1.2 (100ml) was added and it was then shaken for two hours using mechanical stirrer. Solution

was filter using Whatman filter paper. Filtrate was collected and proper dilution of filtrate was made with 0.1N HCl having pH 1.2. Diluted sample was analyzed by using UV/Visible spectrophotometer at ƛ max against 0.1N HCl blank and absorbance was noted. Actual drug encapsulated in total yield muco-adhesive microspheres was calculated from absorbance value with proper dilution factor consideration. The amount of drug loaded and entrapped in the muco-adhesive microspheres was calculated by the following formula Durrani, Davies, Thomas, & Kellaway, 1992),

$$\% \text{ Drug entrapment} = \frac{\text{Amount of drug actually present}}{\text{Theoretical drug load expected}} \text{ X } 100$$

Experiment was performed in triplicates an average value was reported in result and discussion chapter for respective formulation batch.

iv) % Muco-adhesive & Muco-Adhesive time of Microspheres using 0.1 N HCl having pH 1.2

Muco-adhesive time and percentage of muco-adhesion of microspheres were study by using dis-interagation test apparatus. Goat intestinal mucosa was collected from local scouter house. Mucosa was with krebs ringer solution. Mucosa was cut into proper size of glass slide and it was fixed on glass slide with help adhesive gum. Fifty muco-adhesive microspheres was placed on to mucosa and it allow for muco-adhesion with help of dissolution media.

Prepared glass side was placed into disintegration test apparatus tube at an angle of 45 degree which was previously fill with 0.1 N HCl having pH 1.2. Experiment was started and time was noted as time (t=0). Glass slide was removed at regular interval of time for examination of no of muco-adhesive still adhered to goat mucosa with the help of lence. It was used to calculated % muco-adhesion of microspheres. After examination of glass slide, it was again placed to back into dis-interagation test apparatus tube. Procedure was repeated at regular interval time 1, 2, 4,8,12, 24 hours and observation was noted for each time. Experiment was performed in triplicate and result of reported in result and discussion section.

Simultaneously, muco-adhesive times were noted. End point was noted at which time all microspheres was wash-out completely from glass side Durrani, Davies, Thomas, & Kellaway, 1992).

3.*3.9.2 In Vitro* Drug Release Study:-

In Vitro Dissolution Study was determined by using six station dissolution test apparatus using modified procedure than that of tablets dosage form. Temperature of dissolution media was set about $37^0C \pm 2^0C$. Speed of peddle was also set as 50 rpm. Gastro-Retentive muco-adhesive microspheres were placed into muslin cloth bag and this bag was then fixed to peddle with the help of thread. Paddle was fitted to Dissolution test apparatus and it was inserted into dissolution vessel which previously filled with nine hundred millilitres of 0.1N HCl having pH 1.2. Experiment was started and time was noted as time (t=0). One ml sample was periodically removed from dissolution media at different time intervals such as time (t) 1, 2,4,8,12,24 hours. At the same time, equal volume of blank 0.1N HCl having pH 1.2 from stock was added to dissolution media vessel to maintain sink condition. Samples were analyzed by UV spectrophotometer using 0.1N HCl having pH 1.2 as blank at ƛmax . Absorbances were noted for respective sample time. From absorbance value, % cumulative drug release was calculated by considering dilution factor. Experiment was performed in triplicates and average values for % cumulative drug release were noted and reported. From this data, dissolution release profile was constructed as time in hours on x-axis and % cumulative drug release on y-axis[92, 105, 113-116].

Dissolution release profile was reported in result and discussion chapter for respective formulation.

3.3.9.3 Micrometric Properties of Muco-Adhesive Microspheres

a) Bulk Density

Bulk density was determined by tapped density test apparatus. Sufficient quantity of muco-adhesive microspheres was introduced into dry cylinder of tapped density apparatus and care was taken that an apparent volume blend microspheres should be between 50 ml and 250 ml. Record the unsettled apparent volume V_0 to the nearest millilitres and mass of muco-adhesive microspheres was also noted. Bulk density was calculated by simple mathematical formula as follow [92, 117-119].

$$\text{Bulk density} = \frac{\text{Mass of Powder}}{\text{Unsettled Apparent Volume } V_0}$$

Experiments were performed in triplicate and average result with standard deviation is shown in result and discussion chapter of formulation batch.

b) Tapped Density:

After note down the initial volume, the cylinder of tapped density apparatus was operated for tapping, for tapping for 10, 500 and 1250 taps and corresponding volumes V_{10}, V_{500} and V_{1250}. Volume readings were taken until little further volume change is observed. If there was the difference between V_{500} and V_{1250} was found to be greater than 2 ml, and then cylinder of tapped density apparatus was again operated for further tapping for 1250 taps. Corresponding volumes V_{2500} was noted to the nearest millilitre. Tapped density was calculated by simple mathematical formula as follow[92, 117-119].

$$\text{Tapped Density} = \frac{\text{Mass of Powder}}{\text{Settled Apparent Volume } V_T}$$

Experiments were performed in triplicates and average result with standard deviation is shown in result and discussion chapter of formulation batch.

c) Compressibility Index and Hausner Ratio

The compressibility index and Hausner ratio may be calculated using measured values of bulk density (r_{bulk}) and tapped density (r_{tapped}) as follows [92, 117-119].

$$Compressibility\ Index = 100 \times \frac{\rho_{tapped} - \rho_{bulk}}{\rho_{tapped}}$$

$$Hausner\ Ratio = \frac{\rho_{tapped}}{\rho_{bulk}}$$

For the compressibility index and the Hausner ratio, the generally accepted scale of flow ability is given in **Figure No 08**.

Compressibility index (per cent)	Flow character	Hausner ratio
1-10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
> 38	Very, very poor	> 1.60

Figure No 8: Accepted Scale of Flow ability

Experiments were performed in triplicates and average result with standard deviation is shown in result and discussion chapter of formulation batch.

d) Angle of Repose

The angle of repose of muco-adhesive microspheres was determined by glass funnel method. Powders were weighed accurately and passed freely through the funnel so as to form a heap. The height of funnel was so adjusted that the tip of the funnel just touched the apex of the heap. The diameter of the powder cone so formed was measured and the angle of repose was calculated using the following equation [92, 117-119].,

$$\tan \Theta = h/r, \quad \Theta = \tan^{-1}(h/r)$$

Where, θ = angle of repose ,h = height of the pile and, r = radius of the powder cone respectively.

Flow property	Angle of repose (degrees)
Excellent	25-30
Good	31-35
Fair (aid not needed)	36-40
Passable (may hang up)	41-45
Poor (must agitate, vibrate)	46-55
Very poor	56-65
Very, very poor	> 66

Figure No 09: Interpretation of Powder Flow ability Flow ability Using Angle

Experiments were performed in triplicates and average result with standard deviation is shown in result and discussion chapter of formulation batch.

3.3.9.4 Kinetics of Drug Release

Kinetic of drug release of formulation were noted from result given by PSP disso 3 software. Standard calibration data was inserted into PSP disso software for calculation of % cumulative drug release. From dissolution study, absorbance value was noted which was inserted into PSP Disso Software. Detail information of best fit model, Parameters for Korsmeyer-Peppas Equation, various models fitting data Zero order, 1^{s}t order, Matrix, Peppas, and Hix.Crow was given by software.

Kinetic data of drug release was reported in tabular format in result and discussion[92, 120-122].

3.**3.9.6 Scanning Electron Microscopy (SEM):-**

The surface, morphology, size, shape, etc., were determined by using Scanning Electron Microscope. Dry muco-adhesive microspheres were placed on an electron microscope brass stub that was coated with gold (thickness 200 nm) in an ion sputter. Pictures of muco-adhesive microspheres were taken by random scanning the under the reduced pressure (0.001 torr)[27, 123-126].

3.3.9.7 Stability Study

International Conference on Harmonization (ICH) specifies the length of study and storage conditions. Optimized formulation was carried out using stability humidity chamber. Optimized formulation was placed in different temperature-humidity conditions such as 40±2^{0}, 75±5% RH , 25 ^{0}C ± 2 ^{0}C ,75 % ± 5 % RH And 40 ^{0}C ± 2 ^{0}C, 75 % ± 5 % RH . Test sample were drawn from formulation container at regular interval time up to 6 month (2, 4, 6 months) and it was tested for various evaluation parameters such as drug content, muco-adhesion time, cumulative drug release (After 24 Hours). Experiment was performed in triplicates and average values for each evaluation parameters were reported in result and discussion chapter[50, 125, 127-134].

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